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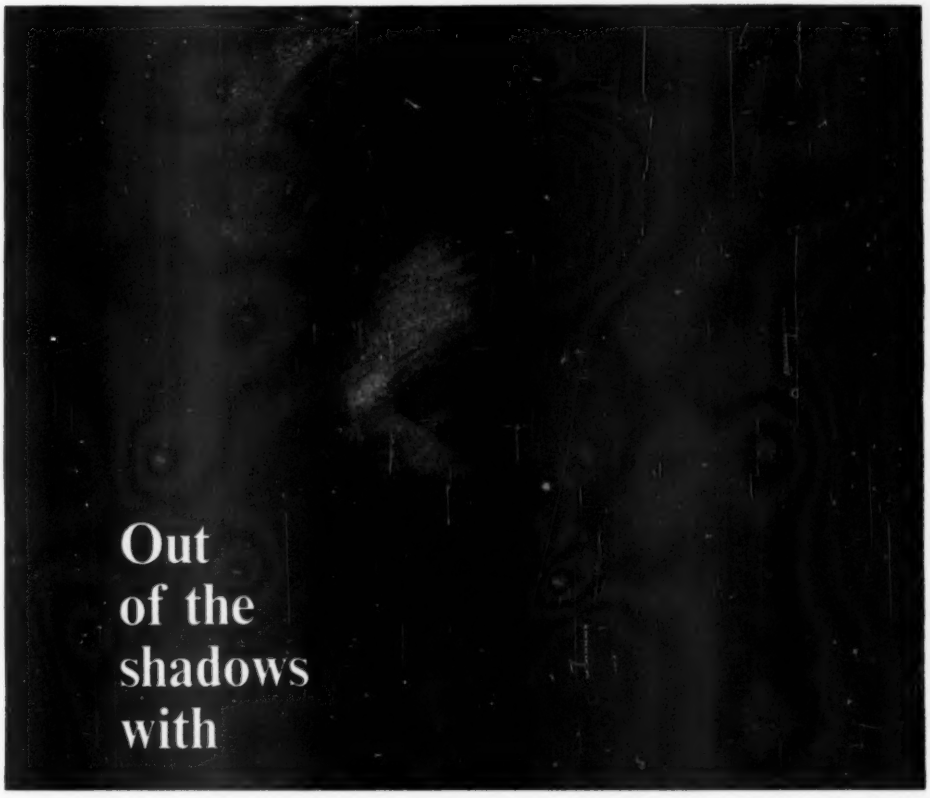

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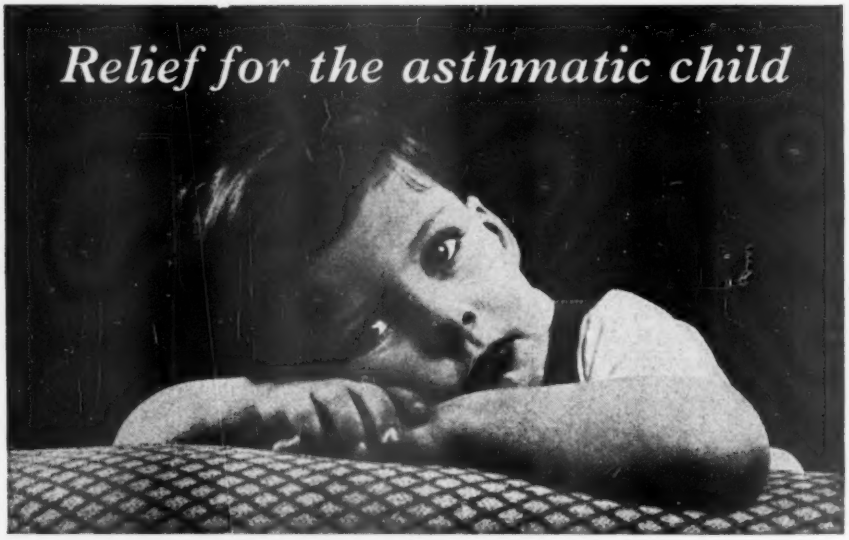

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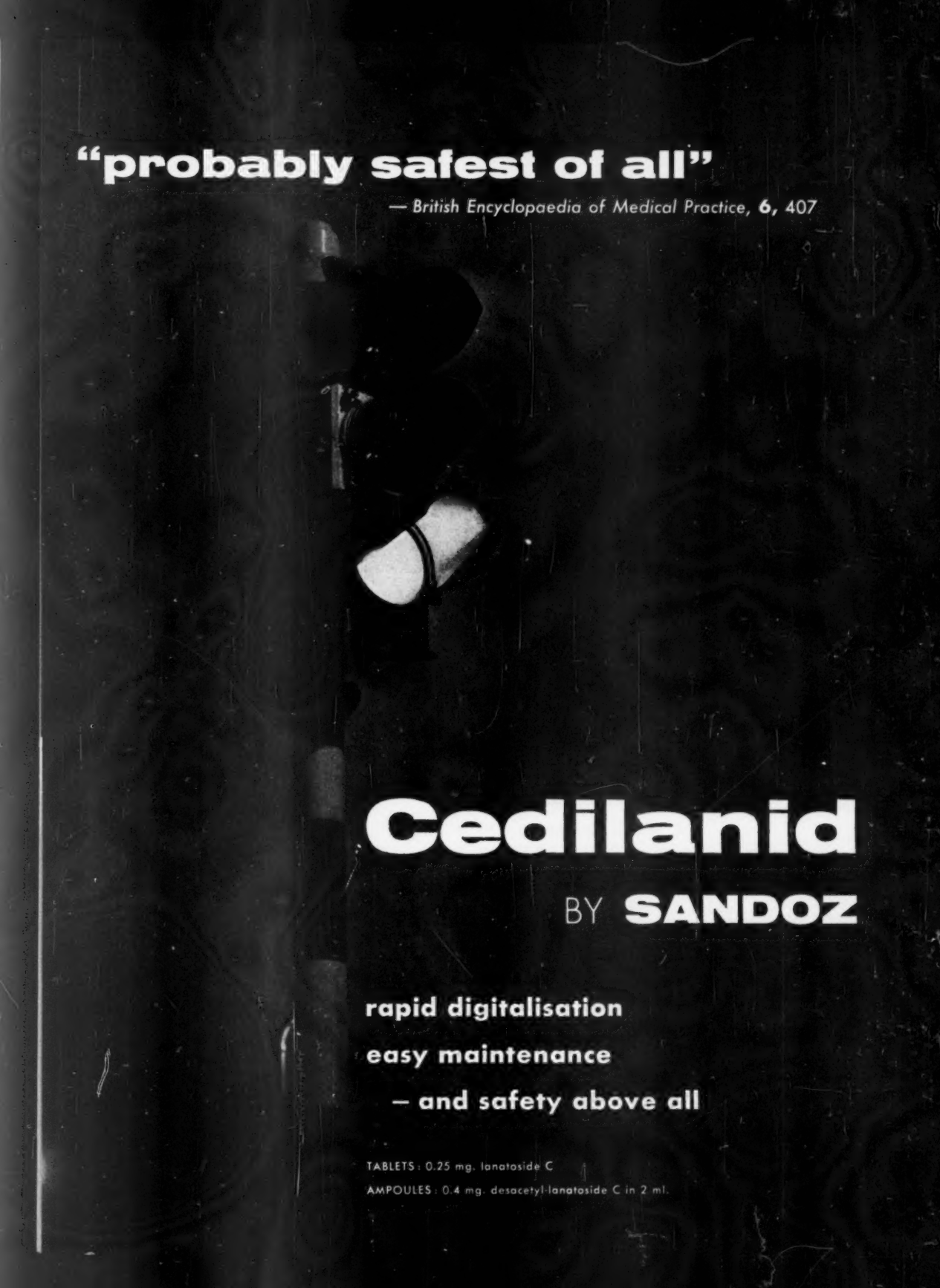
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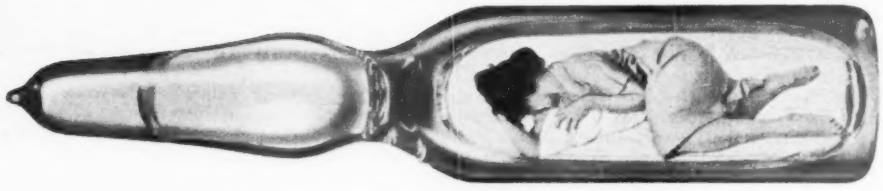

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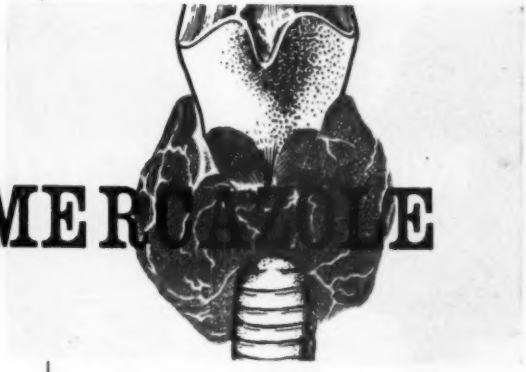

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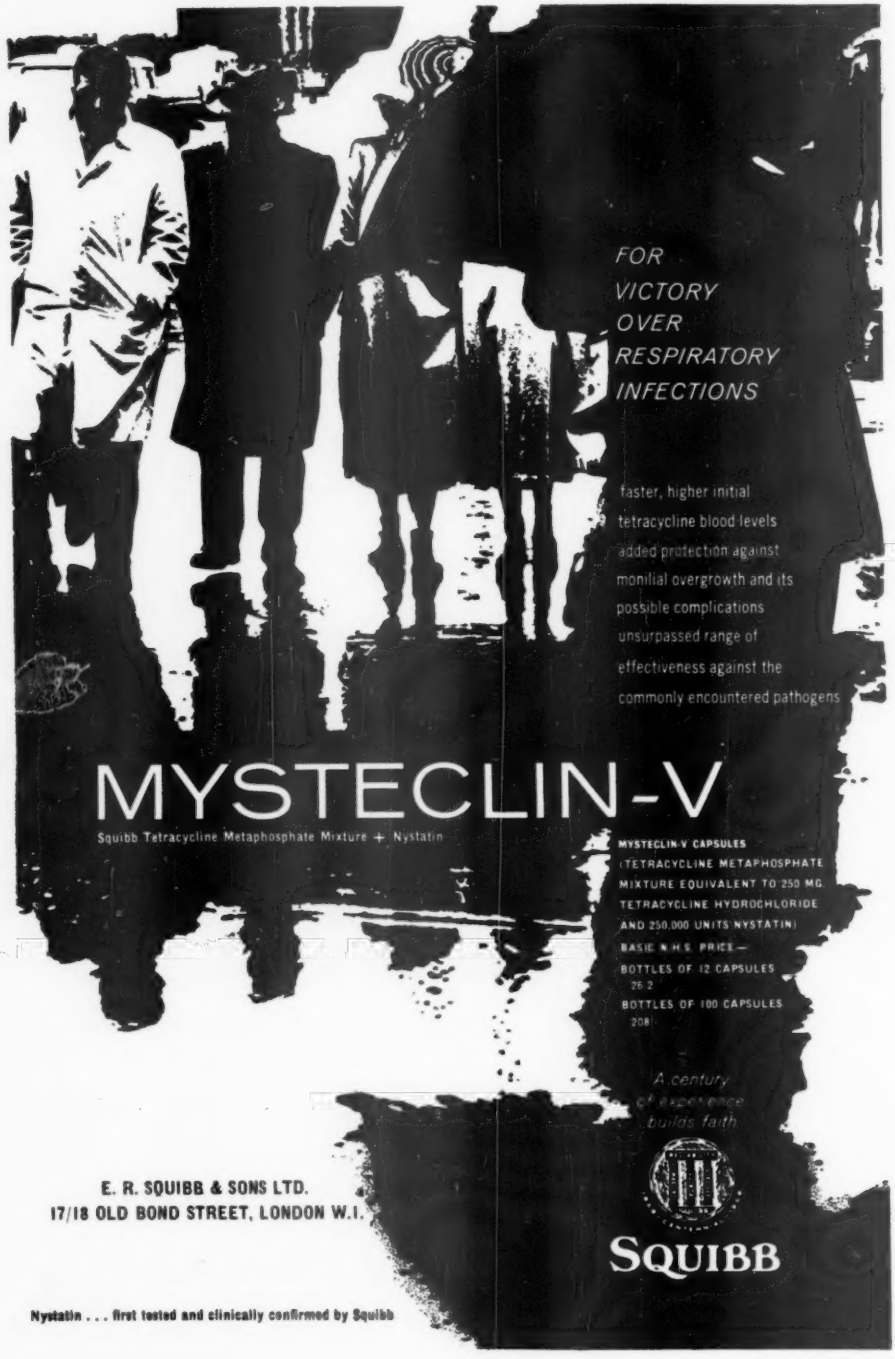
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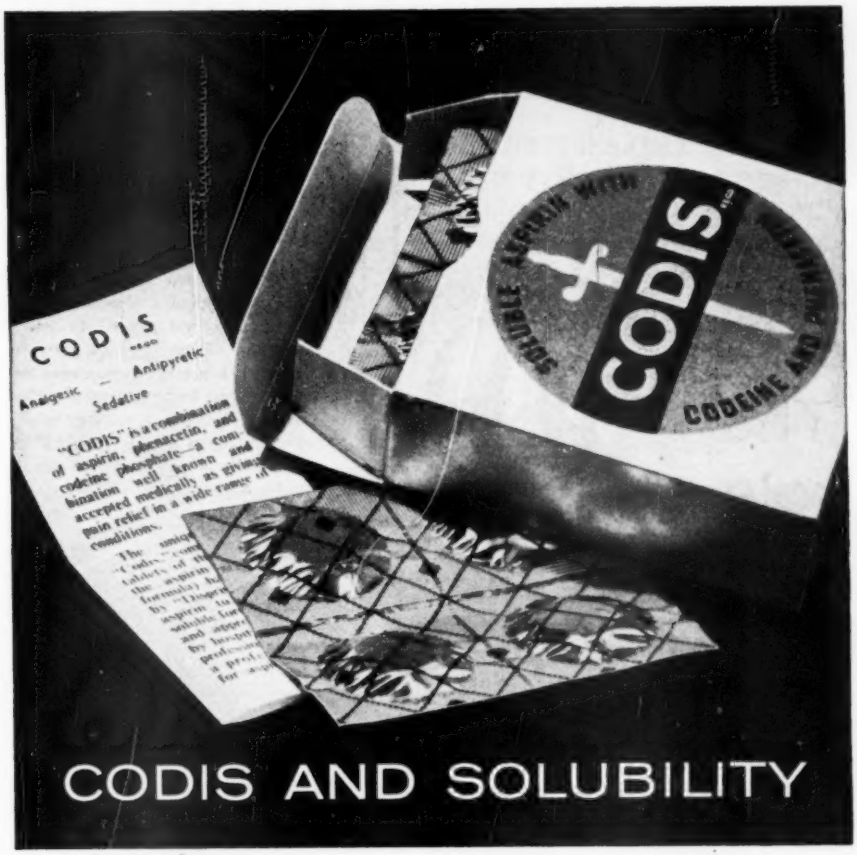

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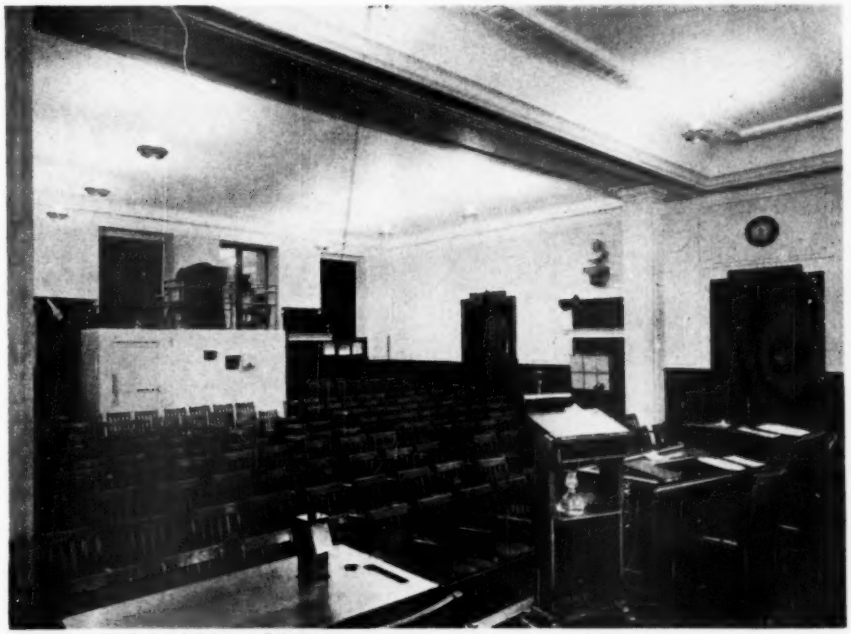

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October 31, 1958

SYMPOSIUM ON DISORDERS OF THE SMALL INTESTINE (EXCLUDING THE DUODENUM)

SECTION I

Chairman—EDWARD R. CULLINAN, M.D., F.R.C.P.

Investigation of the Small Intestinal Function

By E. N. ROWLANDS, M.D., B.Sc., F.R.C.P.

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As this is a clinical symposium, I propose to confine my remarks to studies on human beings and to concentrate on the general problems involved in the investigation of the small intestinal function and on some of the more promising new techniques. I shall comment only briefly on the use of these methods in the investigation of a few clinical problems.

The function of the small intestine is to complete the process of digestion begun in the stomach and to transfer the products from the lumen of the gut into the blood or lymph. Our knowledge of the mechanism of intestinal absorption is rudimentary, but it is gratifying to clinicians that investigation of the malabsorption syndrome is helping to elucidate the physiology of the normal processes. Although it is the only indispensable part of the alimentary tract, there has perhaps been less clinical stimulus to research on the small intestine because it is relatively immune from disease by comparison with the approaches to it from above and below. These also render it virtually inaccessible to direct investigation, and indirect methods which depend on analysis of the stools or blood are unsatisfactory, because so many factors are involved that it is difficult to disentangle the specific functions of the small intestine itself from those of many other organs and tissues. Its digestive functions, for example, are intimately related to and depend upon those of the pancreas and bile, and its absorptive functions depend on the form in which material is presented to it; it cannot absorb vitamin B_{12}, for example, unless the stomach secretes intrinsic factor. There is also the problem of how to separate its digestive from its absorptive functions; for example, there is still considerable controversy as to how far the process of digestion of fat has to proceed within the lumen of the gut before the fat is absorbed. Problems of this kind arise in the clinical investigation of small intestinal function, but the ultimate problem is how substances are transferred across the intestinal cell into the circulation. This is the most complex example of the general problem of the permeability of membranes, in that the intestinal mucosa absorbs such a large number of different substances. Very little is known about it despite many ingenious studies both *in vitro* and *in vivo*, but there is evidence that several cellular mechanisms are involved, and a general theory of absorption cannot be formulated. Simple physical laws of diffusion would explain the absorption of those end-products of digestion whose concentration in the bowel is higher than that in the tissues. Some of these, however, such as glucose and some amino acids, are known to be absorbed by an active, selective mechanism. Other substances are absorbed against considerable concentration gradients. In these days of intestinal biopsy it is possible that the nature of some of these cellular mechanisms of absorption may be unravelled by studies on man, and the mystery of the relation between gluten and cœliac disease provides a challenging stimulus to research on the mucosal lesion. Meanwhile there have been some advances in the investigation of small intestinal function at what I might call the clinical level, and I propose to review some of these.

The methods in common use are indirect, and fall into the two main categories of balance studies, and tolerance tests. In balance studies, a quantitative estimate of absorption is obtained by measuring the amount of a substance excreted in the fæces and subtracting this from the amount given in the diet, the result being expressed as a

percentage absorption. This depends, however, on many factors other than the function of the small intestine, and also on several assumptions, viz. that the gut does not secrete a significant amount of the substance into the lumen, that the bacteria in the fæces do not contain a significant amount of it, that bacterial fermentation of unabsorbed residues does not occur in the large intestine, and finally that it is feasible in clinical practice to relate the fæcal excretion of a substance to the measured intake over a period of time. In tolerance tests, a standard amount of the test substance is given by mouth and the amount absorbed is estimated from changes in the blood level or the amount excreted in the urine. The rate of absorption by the small intestine, however, is only one of many factors which influence the shape of the blood curves, such as the previous diet of the patient and the rate of gastric emptying, and particularly the rate of distribution of the substance into its body spaces and its metabolism in the body. Theoretically it should be possible to obtain some estimate of these factors by injecting the substance intravenously and measuring the rate at which it disappears from the blood, and then correlating this plasma clearance curve with the oral tolerance curve. Ideally the intravenous injection should be given at the same rate as the substance is absorbed from the gut, but this of course is unknown. A modified tolerance test of this kind has been used for studying the absorption of iron (Callender, 1958). The patients were given a dose of labelled iron by mouth at the same time as an intravenous dose of a second isotope of iron, and the rates of disappearance of both the oral and intravenous isotopes from the plasma were then measured; a corrected plasma curve for the oral isotope was thus obtained and the amount absorbed from the gut calculated. A simpler method of improving the specificity of the tolerance test as an index of absorption would be to give a substance which is not normally metabolised in the body but closely resembles natural foodstuffs, e.g. the use of xylose instead of glucose for measuring the absorption of carbohydrates.

Despite their limitations, both balance studies and tolerance tests can give useful information about the absorption of certain substances, but they are unsatisfactory for studying the digestion and absorption of ordinary foodstuffs. For this purpose it is essential to use direct methods of investigation which make it possible to aspirate samples of the contents of the small intestine from different levels during the digestion and absorption of ordinary meals. This would make it possible to determine the relative importance of pancreatic enzymes, succus entericus, bile, pH, and motility in the processes of digestion, and to establish the site of maximum absorption of different foodstuffs. Some data have been obtained in a few special investigations by measuring the rate of absorption of substances from a segment of intestine proximal to an occluding balloon or isolated between two balloons. Cummins and Almy (1953) used this method to study the effect of motility on the absorption of glucose and methionine; the rate of absorption was apparently increased by stimulating motility with a cholinergic drug, but the method was not sufficiently accurate to permit conclusive results.

These cumbersome and unphysiological techniques have been superseded by an ingenious method of intubation described by Blankenhorn *et al.* (1955). A fine polyvinyl tube of about 2 mm. internal diameter is allowed to pass through the entire gastro-intestinal tract, and samples of the contents can be aspirated at any desired level of the small intestine under conditions closely resembling the physiological state. The application of this method is very recent but Borgström and his colleagues in Sweden (1957) have already obtained quantitative data about the extent of digestion and absorption of a well-balanced liquid test meal at different levels of the small intestine in a group of 12 normal subjects. The tube moved slowly downwards during the sampling period and the distance from the nose to the site of aspiration for each sample was noted and this was either localized by X-rays or calculated by reference to data obtained by Hirsch *et al.* (1956). The meal contained fat as corn oil, carbohydrate as glucose and lactose, milk proteins in well-balanced proportions, and a water-soluble reference substance, polyethylene glycol, which is neither absorbed nor digested. From the concentration of this indicator substance in each aspirated sample they were able to calculate, for the first time in man, the percentage absorption of fat, carbohydrate, and protein at different levels of the small intestine. This technique also enabled them to assess the function of the small intestine itself in the processes of digestion. For example, they found that the activity of the enzymes contained in the succus entericus, as represented by invertase and lactase, was insignificant compared with that of the pancreatic enzymes per ml. of intestinal content, and that lactose was absorbed at a level where the disaccharide-splitting enzymes were either absent or in low concentration. These findings, if confirmed, would imply that the enzymes contained in the succus entericus are of little or no importance in the processes of digestion within the lumen of the intestine in man, and therefore their main

site of action is presumably within the mucosal cell. On the other hand, the concentration of the pancreatic enzymes, bile salts and phospholipids was very high in the proximal jejunum which proved to be the main site of digestion and absorption of the test meal. They also obtained data about the rate at which the meal was delivered into the duodenum and its passage through the jejunum and about the dilution of the meal at different levels, and they were able to estimate the degree of mixing of the food and secretions from the ratios of the concentration of the meal and its digestion products to that of the enzymes and bile at different levels. Quite apart from its value in studying the physiology of digestion and absorption, this technique has already proved valuable in a study of intestinal absorption after gastrectomy (Lundh, 1958) because the concentration of the enzymes and their admixture with the meal are of greater interest in such clinical studies than, for example, the data obtained by measuring the response of the pancreas under fasting conditions to injections of secretin and pancreozymin. Incidentally, intubation of the small intestine is the only method of detecting such uncommon causes of malabsorption as the deficiency of bile salts (Ross *et al.*, 1955), or the inactivation of enzymes by the persistence of a very low pH throughout the duodenum and jejunum, as was found in one of Dr. Avery Jones' patients who was suffering from the Zollinger-Ellison syndrome.

Another important advance in the study of the small intestinal function has been the application of radioisotope techniques, some of which I have already mentioned. It is true that these can provide only the same kind of information as chemical methods of analysis because the physiological limitations of balance and tolerance tests are not affected by their use. They also have their own limitations, but when used with discrimination they can make many investigations so much easier to perform that it is possible to carry out a large number of tests in a short time, and to make some studies which could not be carried out in any other way. Their application in this field is so recent that it would be premature to attempt to assess their value, but it is clear that their usefulness depends upon the particular problem under investigation, since there are several mechanisms for the transfer of substances from the lumen of the gut into the circulation. I shall give only a brief review of the investigation of the small intestinal function in relation to a few foodstuffs, mentioning the use of isotopes where relevant.

Absorption of Fat

The absorption of fat has been studied more intensively than that of any other substance, presumably because steatorrhœa is the most obtrusive clinical sign of malabsorption. The detection of steatorrhœa has recently been simplified by the growing realization that rigid balance techniques are not essential, by the use of van de Kamer's rapid method of estimating fæcal fatty acids (Kamer *et al.*, 1949), and also by the application of radioisotope techniques. It has been found that on normal mixed diets of 50–150 grams of fat, the variations in fat excretion are small and the upper limit in normal subjects is about 6 grams per day (Cooke and French, 1958). Most of this is probably derived from sources other than the diet, but the relative proportions of dietary and non-dietary fat that go to form the fæcal fat in any individual patient cannot be estimated satisfactorily. In patients who are taking normal diets it is therefore sufficiently accurate and very much simpler to collect the stools for three to six days and express the results of fæcal fat analysis as grams per twenty-four hours, instead of relating it to intake; and for routine diagnostic purposes it is not essential to use stool markers.

The origin of the fæcal fat is still in doubt because techniques have not been available to assess the proportions derived from the diet and from non-dietary sources such as epithelial debris, bacteria, and excretion of fatty material into the lumen of the intestine. That excretion of fat into the small intestine does not contribute significantly to the fæcal fat in normal subjects is suggested by an observation made by Borgström *et al.* (1957) in their intubation studies. They found that fat in the form of corn oil was absorbed in the first 100 cm. of the jejunum, and in one experiment they labelled the dietary fat by including ^{14}C-triolein in the fat of the test meal and noted that it was not significantly diluted with endogenous fat in the small intestine. New techniques are also being applied to the study of the dietary component of fæcal fat both in normal subjects and in patients with the malabsorption syndrome, by feeding saturated and unsaturated fatty acids labelled with the stable isotope of carbon (^{13}C) and analysing the fæcal fatty acids by partition chromatography and spectrographic methods (Blomstrand, 1958). The evidence at present available indicates that the most important sources of the fæcal fat are the diet and intestinal bacteria, but the application of these techniques is very recent. There is reason to believe, however, that the controversy about the origin of fæcal fat will be settled by these methods and especially by the use of the ^{13}C or ^{14}C isotopes which permit identification of fats without altering their properties.

However, the use of both these isotopes is at present an esoteric research procedure. The only practicable method of labelling fats for clinical studies is with the isotope of iodine (^{131}I), but unfortunately this changes their properties. The use of ^{131}I-labelled fats is therefore an empirical procedure, valuable as a clinical test for detecting steatorrhœa but not for studying the fate of individual fatty acids, because these iodinated fats are not identical with unlabelled fats and may not behave in the same way in the body. There is no reason to doubt that the iodine label remains firmly bound to the fat during its passage through the alimentary tract, but it is split off fairly rapidly after its passage through the intestinal cell (Beres *et al.*, 1957). For these and other reasons, the validity of the use of labelled fats in balance studies is widely accepted, but their value in tolerance tests is debatable, and there are many conflicting reports about the reliability of blood curves as an index of intestinal absorption. Moreover the dose of ^{131}I which is required for the measurement of the blood levels is high enough to discourage repeated tolerance tests in the same subject, whereas in balance tests a dose of 5 μc. or less is sufficient for measuring the fæcal excretion. The labelled triolein is given by mouth and the stools are collected for about three days and passed directly into a container which fits into the counting apparatus. It is essential to avoid contamination with urine since the assumption is that the ^{131}I recovered in the fæces has not been absorbed. This technique measures only the absorption of labelled triolein and not of dietary fat in general, but as a simple clinical test for detecting malabsorption it is probably about as reliable as the chemical method. Neither of these balance techniques can be used to diagnose the cause of steatorrhœa, because it has been shown that an increase in the ratio of neutral fat to split fat in the fæces is not diagnostic of pancreatic steatorrhœa. However, attempts have been made (Reemtsma *et al.*, 1957; Duffy and Turner, 1958) to differentiate pancreatic from small intestinal steatorrhœa by giving oral doses of labelled triolein and labelled oleic acid and measuring the blood concentrations of each. The assumption is that neutral fat cannot be hydrolysed in the absence of pancreatic enzymes, and therefore, in steatorrhœa of pancreatic origin, the labelled triolein is poorly absorbed and the blood curves will be flat, whereas the labelled oleic acid should be absorbed normally. In small intestinal disorders on the other hand the absorption of both the neutral fat and fatty acid is impaired and therefore both the blood curves will be flat. Some observers (Ruffin *et al.*, 1958) have had sufficient confidence in this test to use it for studying absorption in patients after gastrectomy, and have interpreted the combination of flat blood curves for triolein absorption with normal curves for oleic acid absorption as evidence of defective admixture of the pancreatic enzymes with the food. On the other hand some other observers (McKenna *et al.*, 1957) have found blood absorption curves to be unreliable even as a means of detecting steatorrhœa as the following quotation from a recent paper shows (Grossman and Jordan, 1958): "all patients who excreted abnormally large amounts of lipid in the fæces, as determined chemically also had abnormally high levels of radioactivity in the fæces. Blood radioactivity levels were below the normal range in only 4 of 14 patients who exhibited steatorrhœa by the criteria of fæcal lipid content and fæcal radioactivity." The explanation of these divergent views lies partly in the use of ^{131}I as a label for the fats but mainly in the limitations of blood curves as a test of absorption, which I mentioned earlier. No matter what test substance is used, whether radioactive or not, whether fat, carbohydrate or protein, the concentration in the blood is influenced by many factors other than intestinal absorption and it is difficult to define the normal limits. This is probably why such tedious methods as the chemical analysis of blood fats and the counting of chylomicrons after a fatty meal have been largely unrewarding both as clinical tests and in the study of the different phases of fat absorption in man.

Similar considerations apply to the vitamin-A tolerance test, which has been widely used in the diagnosis of malabsorption since the discovery that the blood curves following a standard oral dose of this fat-soluble vitamin were usually flat in patients with cœliac disease. It has been claimed (Legerton *et al.*, 1953) that there is a close correlation between the blood level of vitamin A five hours after an oral test dose and the degree of steatorrhœa, but this has been questioned by others, and Cooke (1958) considers that this level correlates more closely with the degree of malnutrition than with steatorrhœa. The estimation of vitamin A may have some value as a screening test in suspected cases of malabsorption, but the finding of a flat curve in a proved case of steatorrhœa is not very helpful. Before leaving the subject of fat absorption I should mention that despite the use of ^{14}C-labelled fats and the development of ingenious techniques for collecting intestinal and mesenteric lymph in animals, the two main theories of fat absorption are still hotly debated. However, facts are accumulating rapidly and new methods are constantly being developed, the latest being

a technique for cannulating the thoracic duct in man.

Protein Absorption

Apart from a few amino-acid tolerance tests, what knowledge we have of protein absorption in man is based largely on balance studies. These, however, are unsatisfactory because the fæcal nitrogen is not derived from unabsorbed food only but also from bacteria and from endogenous protein contained in the intestinal secretions. It used to be thought that the finding of increased fæcal nitrogen excretion was useful in differentiating pancreatic from idiopathic steatorrhœa, but it has recently been shown (Comfort *et al.*, 1953; Cooke *et al.*, 1953) that nitrogen excretion is likely to be high when there is a large amount of fat in the stools. The fact that the fæcal nitrogen may be as high in idiopathic as in pancreatic steatorrhœa indicates that the nitrogen losses may be derived from endogenous sources as well as from malabsorption of protein.

Carbohydrate Absorption

The balance technique cannot be used to study carbohydrate absorption because any sugars that are not absorbed in the small intestine may be destroyed by bacterial fermentation. However, it has been shown by the intubation method that glucose and lactose are completely absorbed in the first 50–100 cm. of the jejunum. The glucose tolerance test has been widely used as an index of intestinal absorption but the shape of the blood curves is influenced by many other factors. It is true that in idiopathic steatorrhœa the curves are usually flat but this is not invariably so and they may be equally flat in normal people. Equivocal results are therefore commonly found where the clinical diagnosis is in doubt. Indeed the glucose tolerance test is much more valuable as an index of pancreatic disease than of intestinal absorption because blood curves of diabetic type would strongly favour a pancreatic origin for steatorrhœa. For this reason there has been a revival of interest in the use of D-xylose (Benson *et al.*, 1957) which is not normally present in blood and is excreted in the urine. The test is performed by giving 25 grams by mouth and measuring the amount excreted in the urine over five hours. It is claimed that there is only a small overlap of the ranges of values in normals and in patients with idiopathic steatorrhœa. Attempts to correlate the impaired absorption of these and other sugars with defective phosphorylation in idiopathic steatorrhœa have been unsuccessful. The role of phosphorylation in the transfer of sugar across the mucosa is still in doubt.

Absorption of Vitamin B_{12}, Folic Acid, and Iron

Recent studies of the relationship between small intestinal function and anæmia have been so fruitful that it took two days to discuss them at a conference at the Royal College of Physicians last July. To review the findings in a few words: the absorption of vitamin B_{12} can be measured by giving an oral dose labelled with radioactive cobalt and measuring the radioactivity in fæces or urine. If absorption is impaired and cannot be corrected by giving intrinsic factor, some disorder of small intestinal function is likely. If the impaired absorption can be improved by giving antibiotics, there is probably some anatomical lesion of the intestine permitting bacteria to flourish and utilize the vitamin. Absorption is often impaired in cœliac disease and regional ileitis and it cannot be improved by giving intrinsic factor or antibiotics, but may be improved by steroid therapy. When the ileum is affected by disease, however, the impaired absorption cannot be improved by any of these methods because the ileum has been shown to be the main site of absorption of vitamin B_{12} in man (McIntyre *et al.*, 1956; Mollin *et al.*, 1957). This is in contrast to folic acid which is said to be absorbed in the jejunum (Cooke, 1958), and if this is confirmed, the measurement of vitamin B_{12} and folic acid absorption will be invaluable for investigating small intestinal function. The absorption of folic acid has been measured by the urinary excretion test (Girdwood, 1953) and more recently by changes in serum concentration after an oral dose (Chanarin *et al.*, 1958), the patients being saturated with folic acid beforehand to ensure a normal rate of plasma clearance. A valuable method has also been developed for measuring the absorption of iron, by labelling foodstuffs with radioactive iron and measuring the amount excreted in the fæces. It has been found that defective absorption is very uncommon except in patients with steatorrhœa and after gastrectomy.

I am well aware that this brief review is both incomplete and superficial, but I have tried to concentrate on those techniques which have been shown to have some value in the clinical investigation of intestinal function. For example, although I am particularly interested in the new techniques for measuring intraluminal pressures, I do not think that they are relevant to this discussion because we have not yet succeeded in correlating our recordings of motility with the digestive and absorptive functions of the gut. Nor do we know how the intraluminal pressures are related to the tension in the muscular wall of the gut or to the rate of flow of the contents

(Rowlands, 1959). A satisfactory method of measuring the rate of flow is urgently required for the investigation of the common clinical problem of simple diarrhœa. The most welcome advance in this field, however, would be the development of techniques which do not require intubation, and a step has already been taken in this direction. An ingenious method has been described which depends on the use of a small radio transmitter contained in a pill which is easily swallowed and transmits information about pressure, temperature, and hydrogen ion concentration during its passage through the alimentary tract (Mackay and Jacobson, 1958).

REFERENCES

Benson, J. A., *et al.* (1957) *New Engl. J. Med.*, **256,** 335.

Beres, P., Wenger, J., and Kirsner, J. B. (1957) *Gastroenterology*, **32,** 1.

Blankenhorn, D. H., Hirsch, J., and Ahrens, E. H. (1955) *Proc. Soc. exp. Biol., N.Y.*, **88,** 356.

Blomstrand, R. (1958) Abstracts of Scientific Presentations, World Congress of Gastroenterology. Washington; p. 19.

Borgström, B., Dahlqvist, A., Lundh, G., and Sjovall, J. (1957) *J. clin. Invest.*, **36,** 1521.

Callender, S. T. E. (1958) *Lancet*, ii, 257.

Chanarin, I., Anderson, B. B., and Mollin, D. L. (1958) *Brit. J. Hæmat.*, **4,** 156.

Comfort, M. W., Wollaeger, E. E., Taylor, A. B., and Power, M. H. (1953) *Gastroenterology*, **23,** 155.

Cooke, W. T. (1958) *Brit. med. J.*, ii, 261.

——, and French, J. M. (1958) In: Modern Trends in Gastroenterology. Ed.: F. Avery Jones. London; p. 218.

——, Thomas, G., Mangall, D., and Cross, H. (1953) *Clin. Sci.*, **12,** 223.

Cummins, A. J., and Almy, T. P. (1953) *Gastroenterology*, **23,** 179.

Duffy, B. J., and Turner, D. A. (1958) *Ann. intern. Med.*, **48,** 1.

Girdwood, R. H. (1953) *Lancet*, ii, 53.

Grossman, M. I., and Jordan, P. H. (1958) *Gastroenterology*, **34,** 892.

Hirsch, J., Ahrens, E. H., and Blankenhorn, D. H. (1956) *Gastroenterology*, **31,** 274.

Kamer, J. H. van de, Huinink, H. ten B., and Weyers, H. A. (1949) *J. biol. Chem.*, **177,** 347.

Legerton, C. W., Texter, E. C., and Ruffin, J. M. (1953) *Gastroenterology*, **23,** 477.

Lundh, G. (1958) *Acta. chir. scand.*, Suppl. 231.

McIntyre, P. A., Sachs, M. V., Krevans, J. R., and Conley, C. L. (1956), *Arch. intern. Med.*, **98,** 541.

Mackay, R. S., and Jacobson, B. (1958) *Electronics*, **31,** 51.

McKenna, R. D., Bourne, R. H., and Matzko, A. (1957) *Gastroenterology*, **32,** 17.

Mollin, D. L., Booth, C. C., and Baker, S. J. (1957) *Brit. J. Hæmat.*, **3,** 412.

Reemtsma, K., Malm, J. R., and Barker, H. G. (1957) *Surgery*, **42,** 22.

Ross, C. A. C., *et. al.* (1955) *Lancet*, i, 1087.

Rowlands, E. N. (1959) In: Symposium on Quantitative Methods in Human Pharmacology and Therapeutics, 24th and 25th March, 1958. Ed.: D. R. Laurence. London. In press.

Ruffin, J. M., *et al.* (1958) *Gastroenterology*, **34,** 484.

Histopathology of the Small Intestine

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The small intestine, excluding the duodenum, is about 20–25 feet long. The proximal two-fifths is called the jejunum and the distal three-fifths constitutes the ileum. It tends to become narrower throughout its course, but there are also microscopical differences between the jejunum and ileum which will be referred to later.

In its general microscopic structure the small intestine consists of two muscle layers, an inner circular and an outer longitudinal, lined by a mucous membrane and covered externally by visceral peritoneum. The mucous membrane or mucosa is separated from the muscle layers or muscularis externa by a layer of loose connective tissue known as the submucosa. Likewise the peritoneum and muscularis externa are separated by the serosa, also composed of loose connective tissue. In the normal small intestine the mucosa and the peritoneum are freely mobile over the muscularis externa.

The small intestinal mucosa consists of an epithelial membrane and a supporting framework of fine connective tissue known as the lamina propria. These rest on the muscularis mucosæ. The latter consists of smooth muscle fibres together with some elastic tissue. Some of the muscle fibres are longitudinal, others are circular. The muscularis mucosæ is important in the maintenance of the normal mucosal pattern. The submucosa and serosa consist of loose connective tissue and elastic fibres containing the main blood and lymphatic supply to the intestinal wall. In particular, the submucosa contains numerous large veins. Meissner's plexus of post-ganglionic sympathetic nerves together with ganglia is found in the submucosa. Auerbach's plexus of ganglia and preganglionic parasympathetic nerves is found between the two layers of the muscularis externa. The visceral peritoneum covering the small intestine is composed of a thin layer of pavement epithelium supported by a layer of fibrous tissue which contains a well-developed elastic lamina (Fig. 1). Hence the elasticity of the peritoneum.

The small intestine presents an enormous absorptive surface, not only because of its great length, but because the mucous membrane is thrown into crescentic circular folds or plicæ circulares. These are most prominent in the upper jejunum (Fig. 2), gradually becoming smaller towards the lower ileum where they disappear. The absorptive surface is also increased by the intestinal villi, which are most developed in the jejunum, again becoming fewer and shorter towards the lower ileum. There are

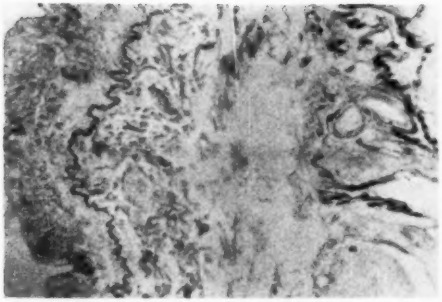

FIG. 1.—Peritoneum showing the wavy elastic lamina stained black by Weigert's method. ×125

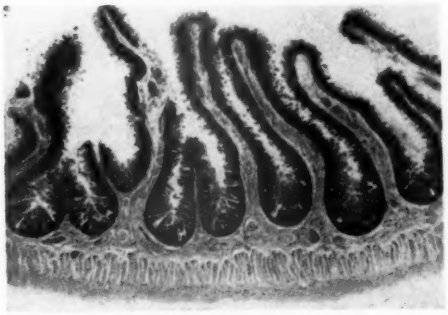

FIG. 2.—Normal jejunum. H. and E. ×2.

anatomical reasons, then, to support the view that the absorptive and secretory power per foot is greater in the jejunum than the ileum. The presence of the plicæ circulares appears to depend on the tone of the smooth muscle fibres of the muscularis mucosæ and on the state of the submucosa. In the normal small intestine dilatation will cause the plicæ to disappear, and contraction to emphasize their presence. But contraction and dilatation are only possible in the presence of a normal elastic submucosa. If the latter is affected by fibrosis, the muscularis mucosæ will be immobilized, leading to atrophy of the plicæ.

The surface cells of the small intestine which cover the intestinal villi are of two types (Fig. 3). Firstly, there are simple columnar cells which are non-secretory and primarily absorptive in function. Between these simple columnar cells may be seen goblet cells, in varying stages of mucus secretion. The simple columnar epithelial cells have a brush border which is really composed of enormous numbers of microvilli which further increase the absorptive capacity of the epithelial membrane: these are only found in small intestinal epithelium. They are absent from the normal stomach mucosa and from

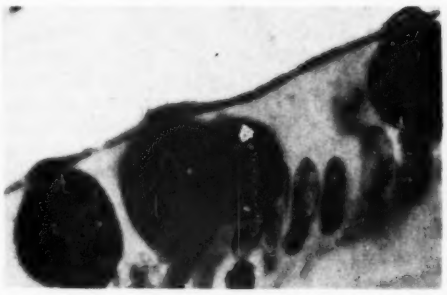

FIG. 3.—Small intestinal epithelium. Simple columnar cells and goblet cells are present. Note the brush border. PAS. ×315.

large intestinal mucosa which is entirely composed of mucus-secreting or goblet cells. Their absence from the colon links up with the relatively greater absorptive power of the small intestine.

The mucus-secreting or goblet cells of the small and large intestine are stained red by mucicarmine. The normal gastric mucosa will not stain with mucicarmine, which suggests that gastric and intestinal mucus differ in their chemical structure.

The experiments by Florey (1958) at Oxford suggest that the functions of mucus are mainly physical, being concerned with lubrication and the protection of the delicate intestinal mucous membrane from damage by solid matter. This is illustrated by the examination of surgical specimens of intestine from patients who have been prepared pre-operatively with non-absorbable sulphonamide. Not infrequently these contain the disintegrating tablets of sulphonamide wrapped up in a neat parcel of mucus.

The deep part of the small intestinal mucosa contains the intestinal glands or crypts of Lieberkühn. These are also lined by simple columnar and goblet cells, except at the base of the crypts where two types of cell of great interest are found. These are the Kulchitsky cells and the Paneth cells.

The Kulchitsky cell has, in recent years, achieved considerable notoriety because of the discovery of the clinical syndrome associated with carcinoid tumours. The cells are found mostly near the base of the crypts of Lieberkühn, although some may be seen nearer the surface of the epithelium. They are low columnar or triangular in shape, with nuclei which are rather larger and clearer than those of the neighbouring cells. The cytoplasm contains granules which are always infranuclear in contrast to the neighbouring Paneth cells in which the granules

are supranuclear. We now know that the granules in the Kulchitsky cells contain 5-hydroxytryptamine and that this substance is secreted into the blood stream. In other words, the Kulchitsky cell is an endocrine cell, and this might explain the basal position of the cytoplasmic granules. The Kulchitsky cells are found throughout the gastro-intestinal tract, but are most common in the duodenum and small intestine. There seems to be no difference in their frequency in the jejunum and ileum.

The granules in Kulchitsky cells and carcinoid tumours may be stained brick red by a diazo dye, the Brentamine fast Red B Salt. They are also strongly eosinophilic in hæmatoxylin and eosin preparations and have the property of reducing ammoniacal silver to metallic silver—in other words they are argentaffin. Hence the term argentaffinoma.

It has been noticed that there is hypertrophy of smooth muscle in the neighbourhood of carcinoid tumours and the suggestion has been made that this is due to the local effect of 5-hydroxytryptamine secretion. However, it is my experience that local hypertrophy of smooth muscle is common in the neighbourhood of diseased intestine, including carcinoma and endometriosis. It is probable that this is a work hypertrophy following interruption of the normal muscular contractions of the intestine by diseased tissue. More evidence must be obtained before the theory can be accepted that the hypertrophy of muscle in the neighbourhood of carcinoid tumours is due to the local action of serotonin.

We know something of the histology and function of the Kulchitsky cell. The other special cell found at the base of the crypts of Lieberkühn remains a complete mystery. This is the Paneth cell.

The Paneth cell (Fig. 4) was first described by Schwalbe in 1872, but the first accurate description was given by the German physician Dr. Paneth in 1888. It is remarkable that we have almost nothing to add to-day to Dr. Paneth's original description of this cell and we are still ignorant of its function.

Paneth cells are found only in the small intestine. They are absent from the normal stomach, although they may be present in areas of intestinal metaplasia. An occasional Paneth cell can be found in the cæcum, but they are absent from the rest of the large intestine. The cells are found only at the base of the crypts of Lieberkühn. Most crypts have at least one cell and often two or three.

Paneth cells contain numerous, rather coarse granules which are supranuclear in position. They are strongly eosinophilic in hæmatoxylin and eosin preparations. A more specific staining

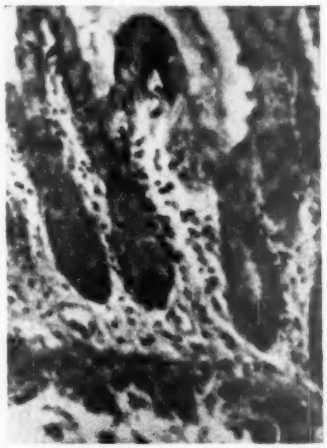

FIG. 4.—Small intestinal mucosa. Paneth cells at the base of the crypts of Lieberkühn. Phosphotungstic acid, hæmatoxylin and mucicarmine. ×105.

technique has been described by Kerr and Lendrum (1936) in which the granules are stained blue-black by phosphotungstic acid hæmatoxylin. The supranuclear position of the Paneth cell granules suggests that they are extruded into the lumen of the crypts of Lieberkühn. However, free granules are not seen in the lumen, although a close study of the periphery of the cell strongly suggests that they are excreted in this direction.

The chemical nature and function of Paneth cell granules is not known. There is no sound evidence for the theory that they are precursors of goblet cells. An increase or decrease in their number and position has not been described in any disease; and unlike the neighbouring Kulchitsky cells, tumours of Paneth cells have never been reported. Our ignorance of this common cell is profound, and is a challenge to future research.

Nodules of lymphoid tissue are present in the lamina propria throughout the small intestine. The smaller are entirely confined to the lamina propria, but larger ones bulge through the muscularis mucosæ into the submucosa. These small nodules are found with greatest frequency in the lower ileum. In addition, the lower ileum contains considerably larger nodules of lymphoid tissue in the mucosa known as Peyer's patches.

Lymphoid tissue plays an important part in the pathogenesis of diseases of the small intestine. It provides a focus of infection for a number of inflammatory conditions. Typhoid and tuberculosis are well-known examples of this—the ulcers being found with greater frequency in the

lower ileum where there is most lymphoid tissue. Likewise, the ileocæcal type of intussusception in infants is possibly due to hyperplasia of the lymphoid tissue in the terminal ileum. There is evidence, too, that Crohn's disease begins in the lymphoid tissue of the small intestine. In the first place Crohn's disease is most common in the terminal ileum. Secondly, the histological appearances are those of a disease of lymphatic tissue. The three main histological features in Crohn's disease are: overgrowth of lymphoid tissue with a characteristic distribution in the submucosa; the formation of fissures which appear to begin in the lymphatic nodules of the mucosa and gradually extend through the intestinal wall; and last, the presence of non-caseating giant cell systems in at least 60% of cases. These resemble the giant cell systems of sarcoid rather than tuberculosis.

It is well known that ectopic epithelium of gastric or pancreatic type may be found in the intestine, particularly within a Meckel's diverticulum. In my experience epithelium of the type found in the pyloric glands of the stomach is not infrequently present in pathological material from the ileum (Fig. 5). Whether this is due to metaplasia or is a congenital abnormality is not clear, although the latter seems the more likely.

It has been stated that the polyps in small intestinal polyposis or the Peutz-Jeghers syndrome may show histological evidence of malignant change, although there has been no report of a patient with this disease dying from primary small intestinal carcinoma. A recent report from the Mayo Clinic (Bartholomew *et al.*, 1957) suggests that these polyps are not neoplasms in the generally accepted sense of the word, but are more in the nature of a congenital abnormality or hamartoma. The histological evidence for this is that the polyps are not composed of one predominant type of proliferating cell. On the contrary all the epithelial cells of the intestinal mucosa, including the simple columnar cells, the goblet cells, and the Paneth cells are represented in the same relationship to one another as they are in the normal mucosa. Furthermore, the stroma consists of bands of smooth muscle fibres, which are related to the epithelial elements of the polyp in the same way as to the normal mucous membrane. If the polyp of the Peutz-Jeghers syndrome is not a neoplasm, but a hamartoma, then it follows that it is not a pre-cancerous condition.

In the wall of the small intestine there is found another cell in which there has recently been a revival of interest. This is the mast cell (Fig. 6), originally described by Ehrlich in 1877. It is a wandering, connective tissue cell filled with granules which stain purple with toluidine blue. These cells have a characteristic distribution in the wall of the small intestine. Most of them are found among the loose connective tissue of the submucosa and serosa in close relationship to the blood vessels. A few may be found in the deeper parts of the lamina propria, close to the muscularis mucosæ, but they are absent from the rest of the mucous membrane. The inner or circular part of the muscularis externa normally contains very few mast cells, but a fair number can usually be found among the fibres of the longitudinal muscle.

It is believed that mast cells secrete heparin (Jorpes, 1946). More recently Riley (1953) and Riley and West (1953, 1955) have shown that they also secrete histamine and the histamine value of a tissue is in proportion to its mast cell content. Certain animals, such as dogs and cattle, develop tumours composed of mast cells and these have a very high histamine

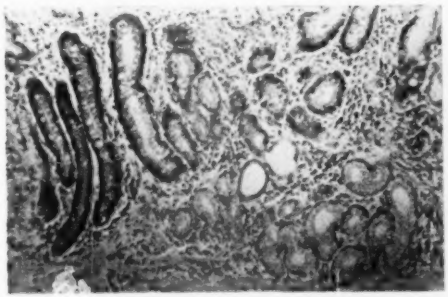

FIG. . —Small intestinal mucosa showing chronic inflammatory changes and tubules of pyloric type on the right of the photograph. H. and E. ×105.

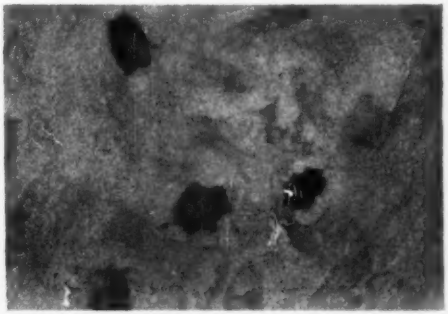

FIG. 6.—Mast cells filled with granules lying in the muscle layers of the small intestine. Toluidine blue. ×315.

content. The injection of histamine causes contraction of smooth muscle and it is tempting to suggest that these cells may be concerned with intestinal motility.

In this paper I have attempted to give an account of the microscopic structure of the normal small intestine together with some remarks on how these appearances may be affected by disease. The large gaps in our knowledge are partly due to the relative inaccessibility of the small intestine to clinical investigation and partly to the fact that pathologists have in the past only had post-mortem material available for study. This is notorious for giving erroneous histological impressions as autolysis of the mucosa occurs very rapidly after death. However, the increasing amount of surgical material available together with the introduction of small intestinal biopsy leads one to hope that the large gaps in our knowledge of small intestinal pathology may be narrowed in future years.

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REFERENCES

BARTHOLOMEW, L. G., DAHLIN, D. G., and WAUGH, J. M. (1957) *Proc. Mayo Clin.*, **32**, 675.
EHRLICH, P. (1877) *Arch. mikr. Anat.*, **13**, 263.
FLOREY, H. W. (1958) General Pathology. 2nd ed. London.
JORPES, J. E. (1946) Heparin in the Treatment of Thrombosis. 2nd ed. London.
KERR, A. B., and LENDRUM, A. C. (1936) *Brit. J. Surg.*, **23**, 615.
PANETH, J. (1888) *Arch. mikr. Anat.*, **31**, 113.
RILEY, J. F. (1953) *J. Path. Bact.*, **65**, 471.
——, and WEST, G. B. (1953) *J. Physiol.*, **120**, 528.
——, —— (1955) *J. Path. Bact.*, **69**, 269.
SCHWALBE, G. (1872) *Arch. mikr. Anat.*, **8**, 92.

Small Intestinal Biopsy: Diagnostic and Research Value

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214 peroral small intestinal biopsies were obtained from 193 patients during the past three years and the method employed (Shiner, 1956) has proved safe and reliable. The tube devised for this purpose (Fig. 1) is a modification of Wood's gastric biopsy tube (Wood *et al.*, 1949) and operates on a similar principle, whereby a knuckle of mucosa is sucked into the aperture at the head-end of the instrument to be cut off by a cylindrical knife within the headpiece which is operated at the tail-end of the instrument. Progress of the headpiece is followed fluoroscopically and biopsy specimens are taken either from the duodenum or upper 12 inches (30 cm.) of jejunum. A recent modification of the headpiece (Fig. 2) by shortening the vertical and horizontal dimensions, together with a longer and more flexible tube, will enable us to biopsy more distal parts of the small intestine.

FIG. 1.—Jejunal biopsy tube—original headpiece.

The method thus described can be used as an out-patient procedure, and takes from half to three hours to accomplish. No special preparation of the patient is necessary other than fasting for at least three hours prior to intubation. In special gastroenterological clinics it may be used routinely. Complications so far encountered consisted of melæna of only moderate amount, not requiring blood transfusion, in 3 of the 193 patients biopsied.

Several mucosal specimens are obtained from the small intestine and gastric mucosa can be biopsied at the same time. These specimens vary from 3–10 mm. in length and include full

FIG. 2.—Jejunal biopsy tube—modified headpiece.

[1]In receipt of a grant from the Medical Research Council.

thickness mucosa, muscularis mucosæ and usually a small amount of submucosa. Jejunal juice collecting inside the tube may be sampled for pancreatic enzyme estimation.

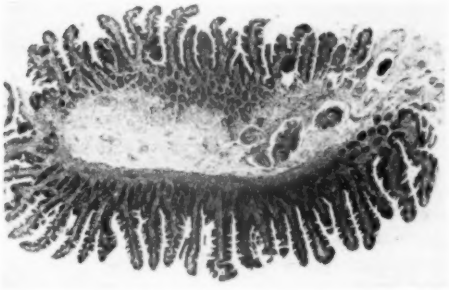

FIG. 3.—Normal jejunal mucosa. H. and E. × 22.

THE NORMAL MUCOSA (Fig. 3)

The mucosal specimens of the duodenum and upper jejunum were studied in 44 patients without obvious disease of the small intestine, as judged by barium meal and follow through, as well as by biochemical tests (Doniach and Shiner, 1957; Shiner and Doniach, 1958). These show on the whole long, narrow villi, though variation in height and width of the individual villus, branching, joining and occasional clubbing are not unusual features. The covering cells of the villi are tall columnar cells with basal nuclei arranged in rather regular fashion. Villous height is roughly two-and-a-half times that of the total mucosal thickness. The rest of the mucosa contains the crypts and glands of Lieberkühn, whose cells show active mitosis and are thought to be the precursors of villous cells. Lymphocytes, plasma cells and a few eosinophils are seen in variable amounts in the villous and interglandular stroma.

MUCOSAL ABNORMALITIES

Interest in the small intestinal mucosa in steatorrhœa was first aroused by Paulley (1954) when he demonstrated mucosal atrophy in 4 patients in whom laparotomy specimens of the small intestine were obtained.

65 patients with steatorrhœa were studied by Shiner and Doniach (1958) and placed into various clinical groups; 10 more have been added since (Table I). The decision as to which type of steatorrhœa the patient belonged to was made on strict clinical, biochemical, radiological and hæmatological grounds and those cases in whom doubt existed were placed into the

TABLE I

Clinical groups	Number of patients
1. Idiopathic steatorrhœa	23
2. Cœliac disease	1
3. Tropical sprue	4
4. Pancreatic steatorrhœa	9
5. Postgastrectomy steatorrhœa	15
6. Steatorrhœa following small intestinal resection	3
7. Jejuno-ileitis with steatorrhœa	7
8. Whipple's disease	2
9. Mild steatorrhœa with marked hypoproteinæmia	2
10. Jejunal diverticulosis with steatorrhœa	1
11. Unclassified steatorrhœas	8
	75

unclassified group. Idiopathic steatorrhœa was further subdivided into:

(*a*) Adult idiopathic steatorrhœa (I.S.) with history of cœliac disease .. .. .. 4 patients
(*b*) Adult I.S. with presumptive history of cœliac disease or family history of I.S... 4 patients
(*c*) Undoubted adult I.S. without history of cœliac disease .. .. 15 patients

Two types of mucosal abnormalities were found in steatorrhœa as a whole (Fig. 4): partial

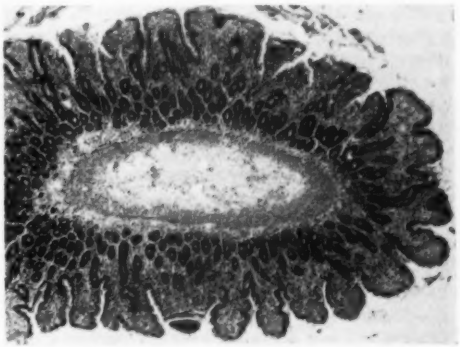

FIG. 4.—Partial villous atrophy. H. and E. × 27.

villous atrophy in which the villi were short and clubbed with a reduction in villous cell height and irregularity of cell nuclei. The mucosal thickness, comprising the glandular layer, however, was increased due to an actual hyperplasia of the glands of Lieberkühn. The ratio between villous height and mucosal thickness was found to be reversed, the average villous height being less than the mucosal thickness. No marked excess of inflammatory cells were observed.

Fig. 5 demonstrates the other abnormality we have called subtotal villous atrophy. The villi are extremely short and flat or non-existent.

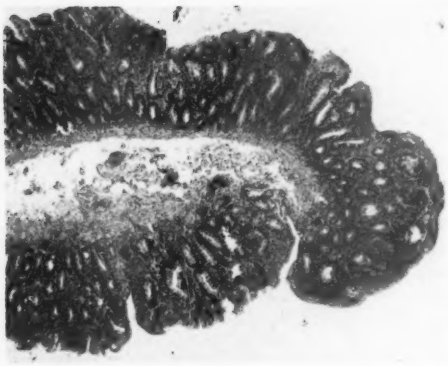

FIG. 5.—Subtotal villous atrophy. H. and E. × 27.

Again there is irregularity of villous cell height and cell nuclei, increase in mucosal thickness and glandular hyperplasia.

Of the 23 patients with idiopathic steatorrhœa, 21 showed subtotal villous atrophy and the remaining 2 partial villous atrophy. Only 2 patients outside the idiopathic group, but excluding the unclassified group, had subtotal villous atrophy. One of these belonged to the postgastrectomy group, the other to the tropical sprue group. Partial villous atrophy, apart from the 2 patients with idiopathic steatorrhœa, was observed in one case with postgastrectomy steatorrhœa, 2 cases of tropical sprue, 1 case of tuberculous enteritis, 1 case diagnosed as a "loop syndrome", and 1 case of malnutrition and steatorrhœa. All these 6 patients in whom the diagnosis was not idiopathic steatorrhœa had macrocytic anæmia at the time of biopsy. In 5 of these, repeat biopsies were carried out after treatment and showed villous regeneration. The preparation used in all cases was folic acid. By contrast, repeat biopsies in the idiopathic group after treatment with folic acid, vitamin B_{12}, gluten-free diet, antibiotics or steroids, either singly or combined, failed to show any histological improvement.

Sakula and Shiner (1957) reported the only case of cœliac disease subjected to small intestinal biopsy. The mucosa showed subtotal villous atrophy, not improved by five weeks' treatment with gluten-free diet as shown by repeat biopsy. Eighteen months later, however, repeat biopsy showed possible improvement.

Normal mucosal biopsies were obtained from all of 9 patients with pancreatic steatorrhœa, and all of 7 patients with jejuno-ileitis accompanied by steatorrhœa. Only 2 of the 15 patients with postgastrectomy steatorrhœa showed an abnormal mucosa. In the remaining 13 normal mucosal pattern was seen. In the 2 cases of suspected Whipple's disease, or intestinal lypodystrophy (Fig. 5), small intestinal biopsy showed mucosal infiltration with macrophages giving the classical staining reaction to periodic acid Schiff.

Diagnostic Application of Small Intestinal Biopsy

The clinical diagnosis of idiopathic steatorrhœa is arrived at by a process of exclusion. The term simply means that no cause for the steatorrhœa has been found. It has often been argued whether idiopathic steatorrhœa constitutes a clinical entity at all or whether it embraces a multitude of conditions under the same name. In this term we include those adults in whom we obtain a clear history of cœliac disease in childhood as well as those in whom the onset of steatorrhœa and other clinical symptoms does not occur until an advanced age. The distinction between idiopathic and pancreatic steatorrhœa is not always clear on clinical grounds and pancreatic function tests are notoriously difficult to interpret. Diverticuli of the small intestine giving rise to steatorrhœa may be missed on X-ray of the small bowel and the differential diagnosis between idiopathic steatorrhœa and regional ileitis or jejunitis may likewise present difficulties. It is not impossible that partial gastrectomy could trigger off symptoms in a patient with "latent" idiopathic steatorrhœa and indeed some evidence to this effect was demonstrated (by Dr. D. L. Mollin) by malabsorption of vitamin B_{12} with and without addition of intrinsic factor in our postgastrectomy patient in whom subtotal villous atrophy was seen on first and several repeat biopsies.

The 23 patients clinically placed into the idiopathic steatorrhœa group represent perhaps the most homogeneous group of idiopathics one could hope for, the doubtful cases being regarded as unclassifiable. This group was used as a basis for histopathological studies. It is therefore not surprising that villous atrophy was uniformly found. This picture of villous atrophy and glandular hyperplasia is non-specific, pathologically speaking and may well represent an end-result of an unknown primary process. It is, however, confined to the steatorrhœa group, as judged by present experience of biopsies taken in various diseases affecting the small bowel, and more specifically to a certain group of steatorrhœa which we have called idiopathic. A further distinguishing feature is its irreversibility after treatment. It is too early to state dogmatically that villous atrophy will be found in all patients in whom no obvious cause for their steatorrhœa

can be found, even after most careful search which might include diagnostic laparotomy.

Because a clinical basis of classification of the idiopathic steatorrhœa is too uncertain, and this includes, at the present state of our knowledge, a classification according to response to gluten-free diet, I should like to suggest a classification of steatorrhœa based on pathological grounds (Table II). Such a classification, though incomplete, would have its greatest usefulness in the diagnosis of that group of steatorrhœa hitherto loosely put together under the label "idiopathic".

TABLE II.—SUGGESTED CLINICO-PATHOLOGICAL CLASSIFICATION

1. *Steatorrhœa with intramucosal abnormalities*
   - (*a*) Idiopathic steatorrhœa—irreversible
   - (*b*) Cœliac disease—? reversible
   - (*c*) Certain secondary steatorrhœas with macrocytic anæmia (including tropical sprue)—reversible
   - (*d*) Whipple's disease
2. *Steatorrhœa without intramucosal abnormalities*
   - (*a*) Pancreatic steatorrhœa
   - (*b*) Most postgastrectomy steatorrhœas
   - (*c*) Jejuno-ileitis with steatorrhœa

The finding of a characteristic mucosal appearance in the 2 cases of Whipple's disease suggests another diagnostic application of peroral mucosal biopsy. This has been confirmed by other workers in America, using the same technique. The patient would not only be spared a diagnostic laparotomy, but would also be given the chance of early treatment with steroids which, according to some authors (Wang *et al.*, 1956), are more effective in the early stages of the disease.

RESEARCH POSSIBILITIES OF SMALL INTESTINAL BIOPSY

Equally interesting are the possibilities for research into the small intestinal function. The influence of folic acid on villous cell regeneration, as observed in some of the cases with macrocytic anæmia described, deserves further investigation. We have noted that villous atrophy is associated with an actual hyperplasia of the glands of Lieberkühn. It is known that the gland cells, by continuous division, are responsible for villous cell formation. Mitosis, a conspicuous feature of the gland cells, is absent in the villous cells. The turnover of cells at the glandular level is one of the most rapid in the body and comparable to that found in the hæmopoietic cells of the bone-marrow. Repeat biopsies three to four weeks after commencement of folic acid therapy in those patients with previous partial villous atrophy and macrocytosis showed increased mitosis in the gland cells coincident with villous regeneration. This suggests a deficiency state of folic acid, local or general, at the glandular cell level where folic acid is required for nucleosynthesis. Further support of this theory is found in the villous atrophy observed by Vitale *et al.* (1954) in rats, following the administration of Aminopterin (4-amino-pteroyl-(L) + glutamic acid).

Small intestinal mucosal biopsy should be carried out in patients receiving Aminopterin in myeloid leukæmia and also on patients developing folic acid deficiency following anti-convulsive drug therapy (Hawkins and Meynell, 1958). The anæmias of tropical sprue, pregnancy and malnutrition associated with macrocytosis and folic acid deficiency should likewise be investigated by intestinal biopsy before and after treatment with folic acid.

Despite the outward similarities of the villous atrophy and glandular hyperplasia in idiopathic steatorrhœa to that observed in the secondary steatorrhœas with macrocytosis as described, except for one of degree, we find the mucosa in the former insensitive to folic acid. This occurs in spite of the findings by Chanarin *et al.* (1958) that malabsorption of folic acid occurs in idiopathic steatorrhœa. It is possible that the difference lies in the advanced stage of villous atrophy as found predominantly in this group or, perhaps more likely, in the lack of an additional factor, as yet unknown, which is necessary to bring about normal villous cell formation. In this connexion it may be recalled that the elimination of gluten from the diet of idiopathic steatorrhœa patients, although accompanied by considerable clinical, hæmatological and biochemical improvement, fails to alter the histological picture. Much interest lies in the mucosal pattern in cœliac disease; our case showed mucosal atrophy. It is possible that here the histopathological changes in the early cases could be reversed by gluten-free diet which is so uniformly effective clinically. Although definite proof was lacking in our case after five weeks of this diet we were satisfied that gluten-free diet had produced minor changes in the appearances of the small intestinal mucosa after eighteen months.

Finally it seems worth while to discuss certain "negative" but none the less important observations which have emerged from this biopsy study. Much has been said and written on the subject of duodenitis in connexion with duodenal ulcers, pancreatic or cholecystic disease and of jejunitis, particularly in connexion with regional enteritis. In our studies (Doniach and Shiner, 1957; Shiner and Doniach, 1958) we have been unable to recognize any specific disease entity in which mucosal infiltration has been the

prominent feature. This is in contrast to gastric mucosa where inflammatory cell infiltration is at least a well-defined pathological feature. Further comparison between biopsy specimens obtained from the stomach and small intestine of any one patient has confirmed the impression that these two types of mucosæ are, pathologically speaking, differently affected by the same disease. For example, atrophy of the gastric mucosa in pernicious anæmia was associated with normal small intestinal mucosa in all of 8 patients investigated. 6 patients with idiopathic steatorrhœa, in whom partial or subtotal villous atrophy was shown on small intestinal biopsy, were found to have, with one exception, normal gastric mucosal biopsies.

It is well recognized that detailed study of autopsy material of the small intestinal mucosa is impractical owing to rapid setting in autolysis and that laparotomy specimens of this tissue are too rarely obtained to be of use for research purposes. With the peroral biopsy technique we can obtain, for the first time, adequate mucosal tissue suitable for detailed histological, histochemical and electron-microscopical studies. Another interesting new field for research could be found in autoradiographic studies of the mucosal specimens following radioactive labelling of fats or folic acid. In this way it is hoped to achieve new understanding of the function of the small intestine as well as its behaviour in disease.

SUMMARY

The technique of obtaining peroral small intestinal mucosal biopsies is discussed. The appearance of the normal mucosa is compared with the pathological findings of villous atrophy, partial or subtotal, found in various types of steatorrhœa only. The diagnostic and research applications of the method are outlined. Certain "negative" but important findings are described.

Acknowledgments.—Most of the histopathological studies mentioned in this paper were carried out by Dr. I. Doniach to whom grateful acknowledgment is hereby made. I also wish to thank Dr. F. Avery Jones and the various clinicians from other hospitals for generously referring their cases to me for the purpose of this study.

REFERENCES

CHANARIN, I., ANDERSON, B. B., and MOLLIN, D. L. (1958) *Brit. J. Hæmat.*, **4**, 156.

DONIACH, I., and SHINER, M. (1957) *Gastroenterology*, **33**, 71.

HAWKINS, C. F., and MEYNELL, M. J. (1958) *Quart. J. Med.*, **27**, 45.

PAULLEY, J. W. (1954) *Brit. med. J.*, ii, 1318.

SAKULA, J., and SHINER, M. (1957) *Lancet*, ii, 876.

SHINER, M. (1956) *Lancet*, i, 17.

——, and DONIACH, I. (1958) Proceedings World Congress of Gastroenterology, Washington. In press.

VITALE, J. J., ZAMCHECK, N., DIGIORGIO, A. B., and HEGSTED, D. M. (1954) *J. Lab. clin. Med.*, **43**, 4.

WANG, C. I., JANOWITZ, H. D., and ADLERSBERG, D. (1956) *Gastroenterology*, **30**, 475.

WOOD, I. J., DOIG, R. K., MOTTERAM, R., and HUGHES, A. (1949) *Lancet*, i, 18.

Radiology in Diseases of the Small Bowel

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THE main methods of radiological investigation available in the examination of the small intestine are plain radiography of the abdomen and barium contrast examinations using techniques appropriate to the condition suspected.

A clinician referring a patient for radiological investigation of the small bowel should have definite possibilities in mind and should communicate these to the radiologist before he commences the examination, otherwise much small bowel pathology is missed. Close clinical and radiological collaboration is infinitely better than a spate of requests for "routine barium meal and follow-through, please". Detailed small bowel examination is time-consuming, wearisome and expensive. Fragmentary examination may miss the crucial point very easily.

Patients with small bowel disorders commonly present for radiological examination on account of abdominal pain or discomfort, obstructive symptoms (vomiting, &c.) or diarrhœa. Less often they are referred on account of frank or occult melæna, anæmia secondary to this or to a deficiency state, or an abdominal mass, or for some complication of the primary condition (as for example pneumaturia due to vesical fistula).

I shall describe a series of cases related to prime symptoms in which radiological investigations may play an important part in the diagnosis.

CASES WITH ABDOMINAL PAIN AS THE IMPORTANT PRESENTING SYMPTON

Case I.—A young man of 26 returning home late at night rode his motor-cycle into a brick left on the road. He was thrown forward on to his handle bars, striking his lower abdomen. He was admitted to hospital with multiple abrasions and complaining of lower abdominal pain. Close examination did not at first suggest any intra-abdominal lesion and it was twenty hours later that he was radiographed.

The films show jejunal distension and free gas beneath the diaphragm. Laparotomy at twenty-four hours revealed two one-inch diameter perforations in the jejunum, just beyond the duodeno-jejunal flexure. A limited resection was performed successfully. The discovery of free gas beneath the diaphragm was recorded in the notes with a mark of exclamation.

Post-gastrectomy pain is most often due to stomal ulcer and the pre-operative diagnosis is predominately radiological. Recurrent stomal ulcerators present their own peculiar difficulties.

Case II.—Duodenal ulcer symptoms began in 1940 when the patient was 16. Perforation and hæmatemesis occurred in 1942. A partial gastrectomy was performed in 1948. A second partial gastrectomy and vagotomy followed in 1950. A gastrocolic fistula developed in 1952 and he had an operation for its closure. A second vagotomy for stomal ulcer was performed early in 1954, and a third subtotal gastrectomy was carried out later that year. A total gastrectomy was performed in 1955. All the gastrectomies except the first were for proved stomal ulcer. For the past three years he has been suffering from steatorrhœa and has recently been in hospital again. Large stomal ulcers were demonstrated after each partial gastrectomy and his gastrocolic fistula was shown by barium enema examination.

Case III.—A man of 35 had a three-year duodenal ulcer history with looseness of the bowels and occasional melæna. A barium meal examination showed a large jejunal ulcer (Fig. 1) with constriction of the lumen and œdematous thickening of the jejunal mucosa, a hypersecretion effect. There was well-marked clumping of barium in the lower ileum resembling a steatorrhœa. Three weeks after total gastrectomy the small bowel appearances had returned almost to normal.

Case IV.—A woman of 47 years was thought to be suffering from Addison's disease on account of her lassitude, hypotension, pigmentation and amenorrhœa. She had bouts of griping abdominal pain. Barium meal examination showed a Crohn's lesion in the ileum and two years later duodenal intubation and small bowel enema, using the technique of Schatszki (1943), showed the lesions to better advantage.

Case V.—I am indebted to Dr. Martin Spiro for this case (Spiro, 1954). An elderly woman complained of abdominal pain for three years and more recently of melæna. A barium meal examination was negative but a small bowel enema through a duodenal tube showed an annular constriction in the upper jejunum without any hold-up. Resection of a jejunal carcinoma was later carried out.

Case VI.—A woman of 26 had had abdominal pain and diarrhœa for three years. Barium meal examination showed constricted areas in the jejunum with destruction of mucosal pattern due to Crohn's disease (Fig. 2).

Case VII.—A boy of 17 had abdominal pain for three years with alternating constipation and diarrhœa. Two years before the examination he had an ileo-transverse colectomy, for Crohn's disease in the ileum. Recently he had frequency and pneumaturia. A barium meal demonstrated lower ileal constriction and some filling of the sigmoid colon from the ileum. A barium enema examination showed involvement of the sigmoid and a track leading from it towards the ileum which was later

FIG. 1 (*Case III*).—A man of 35 years with a large peptic ulcer of the jejunum. Note the associated constriction and hypertrophy of the mucosal folds.

FIG. 2 (*Case VI*).—A woman of 26 years with multiple strictures in her jejunum due to Crohn's disease.

filled from the sigmoid, thus confirming the presence of an ileo-sigmoid fistula. The vesical fistula was not shown.

Ileal and sigmoid disease is commonly associated in Crohn's disease and may well be due to contact involvement.

Cases with Obstructive Symptoms

Among these are some neonatal cases in whose investigation I have been happy to be associated with Dr. J. Sakula.

Case VIII.—A 4-day-old baby, who on day 1 passed a little meconium but none thereafter, commenced vomiting on day 3. On day 4 the vomit was blood-stained and abdominal distension was present. Plain films of the abdomen showed enormous dilatation of the small bowel and meconium was visible in the loops. Laparotomy on day 4 showed huge dilatation of the small bowel as far as the ileo-cæcal junction with volvulus of it. The large bowel was empty. Attempts to empty the gut failed and death occurred on day 5. Autopsy showed fibrocystic disease of the pancreas.

Case IX.—A full-term infant vomited with every feed from birth and the vomit became bilious. On day 5 the abdomen was somewhat distended. A plain film of the abdomen showed that the distension was gastric and duodenal only and very little gas was visible elsewhere. A barium feed showed total obstruction in the distal duodenum which was drawn downwards. Laparotomy by Mr. J. D. Fergusson showed a 360-degree volvulus of the small bowel with tight adhesions at the duodeno-jejunal flexure. The small bowel and colon were collapsed. The adhesions were divided, the volvulus undone and immediately the small bowel began to dilate: subsequent progress was good.

Case X.—A 2-day-old girl had had a normal delivery but at birth the liquor amnii was excessive in amount and was deeply yellow in colour. The infant vomited immediately a large quantity of fluid resembling the liquor and continued to do so for the whole of day 1. On day 2 she was vomiting darker fluid and the abdomen was distended. Meconium was not passed and rectal examination showed some granular fæcal material.

The family history was interesting. Her mother had had infantile pyloric stenosis operated upon at 5 weeks old and a maternal aunt had a congenital volvulus of the small bowel operated upon successfully in the neonatal period.

Plain films of the child's abdomen showed distended small bowel with fluid levels (Fig. 3). Laparotomy by Mr. J. W. P. Gummer revealed atresia of the ileum about 18 in. (45 cm.) above the ileo-cæcal junction. Resection of 12 in. (30 cm.) of ileum was required as gangrene was present in the bowel above the obstruction. Progress was good.

Case XI.—A 5-week-old infant was normal at birth and for two weeks thereafter. Transitory bilious vomiting lasted for a few hours on the fourteenth day. Recovery was apparently complete and normal feeding continued to the age of 4 weeks when bilious vomiting returned and persisted. There was no gross abdominal distension. Barium feed showed dilatation of the stomach and duodenum to the middle of the third part where obstruction was almost complete. The small bowel was shown collapsed, a very little colon gas was seen. Laparotomy by Mr. T. G. I. James showed malrotation of the small bowel with abnormal cæcal and jejunal fixation. This was corrected and progress was excellent.

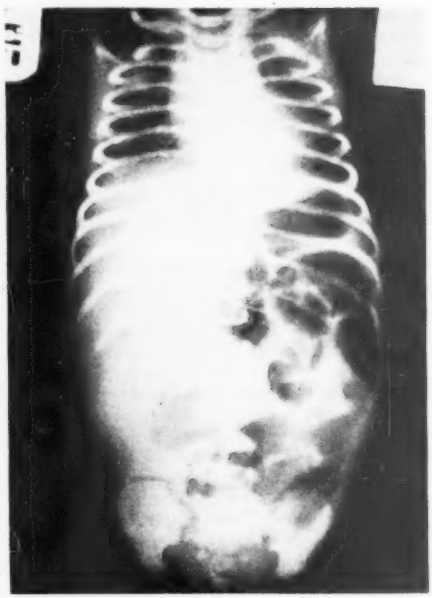

Fig. 3 (*Case X*).—A 2-day-old infant with ileal obstruction due to atresia.

Spontaneous remission of symptoms may be a feature of adult small bowel volvulus also.

Case XII.—A man of 60 was admitted with severe pain in the right iliac fossa with vomiting of four hours' duration; there was accompanying tenderness and rigidity. Laparotomy revealed no abnormality and a normal appendix was removed. There was no pain post-operatively and bowel sounds were audible but bowel action was unsatisfactory and abdominal distension developed. Suddenly on the eighth day the wound burst discharging pus and the patient collapsed. Plain films of the abdomen then showed gross distension of the small bowel with fluid levels present, the loops of small bowel were in the right side of the abdomen. Laparotomy revealed volvulus of the whole of the small bowel except for

the upper 2 ft. (60 cm.) and lowermost 6 in. (15 cm.). Progress was extremely unsatisfactory with death in the eighth week.

In some instances it is possible to see the obstructing cause in the plain film of the abdomen.

Case XIII.—A woman of 60 years was admitted with subacute obstruction which became acute twenty-four hours later. Plain films of the abdomen showed an irregularly rounded intraluminal mass proximal to which the small bowel was distended, and beyond which there was no gas shadow (Fig. 4). At

FIG. 4 (*Case XIII*).—A woman of 60 years with jejunal obstruction due to an impacted concretion of food debris.

laparotomy this mass was found to be an impacted concretion of food debris associated with a local area of jejunitis which was not visible at a barium meal examination two months later.

Gas in the biliary tract with a small bowel obstruction usually implies impacted gall-stone as a cause, unless an artificial fistula with the biliary tract is known to be present.

Case XIV illustrated the presence of gas in the biliary tract due to small bowel obstruction by gall-stones.

Case XV.—Small bowel neoplasm producing an obstruction may simulate simpler causes as in a man of 65 with a carcinoid of his terminal ileum.

Cases Presenting with Diarrhœa

Case XVI.—A woman of 27 had 18 ft. (5·4 m.) of small bowel resected for a massive mesenteric thrombosis two years before I examined her. She had twelve or more offensive stools daily and her hæmoglobin was 30%. Barium meal examination showed the whole of the remaining small bowel and proximal colon outlined within fifteen minutes. There was no time for absorption to take place,

Extensive small bowel diverticulosis is often accompanied by steatorrhœa-like symptoms.

Case XVII.—A man of 80 years had persistent diarrhœa and anæmia for two or three years. Barium meal examination showed innumerable diverticulæ in the small bowel (Fig. 5) and the presence of these was confirmed at autopsy. Death was due to intercurrent bronchopneumonia.

Case XVIII.—The case of a woman of 70 years in whom many much larger diverticula were present, was reported by Scott (1950).

The fluid levels in these large diverticulæ may give rise to the erroneous radiological suggestion that the patient is obstructed.

Case XIX.—Steathorrœa appearances were well shown in a man of 48 years whose diarrhœa followed pancreatectomy for carcinoma. Similar appearances were illustrated in 2 cases of idiopathic steatorrhœa in women of 66 and 72 (*Cases XX and XXI*).

Crohn's Disease

Table I summarizes the incidence of Crohn's

TABLE I.—Age and Sex Incidence of 60 Cases of Crohn's Disease Seen 1948–1958

	Male	Female	Total
Under 25 ..	9	5	14
25–34	6	9	15
35–44	8	7	15
45–54	4	5	9
55–64	1	5	6
65–74	Nil	Nil	Nil
75–84	Nil	1	1
85 and over ..	Nil	Nil	Nil
Totals	28	32	60

disease in my experience over the ten-year period 1948 to 1958. Cases are equally numerous by decades to the age of 45 and the sex distribution is nearly equal. The following illustrative cases presented with diarrhœa.

Case XXII.—Barium enema examination in a man of 24 with two years' symptoms showed lower ileal and right colon involvement. Laparotomy and ileocolectomy followed, but five years later a barium meal examination showed ileal involvement proximal to the anastomosis.

Case XXIII.—A man of 22 with symptoms for two years; his barium meal examination exemplifies one of the practical difficulties in the diagnosis. The small bowel above the area grossly involved was dilated and reluctant to empty and so the worst affected area was difficult to demonstrate. Prolonged observation showed no change in the distribution of the barium, subsequent passage through the constricted area was rapid and it would have been easy for the favourable moment for its examination to have been lost.

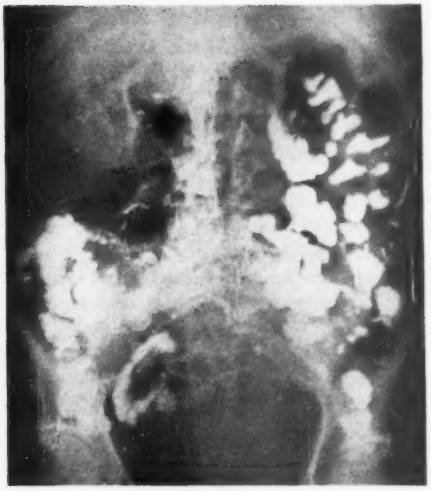

FIG. 5 (*Case XVII*).—A man of 80 years with a very large number of diverticula in his small bowel.

FIG. 7 (*Case XXXI*).—A man of 83 years with calculi in a Meckel's diverticulum.

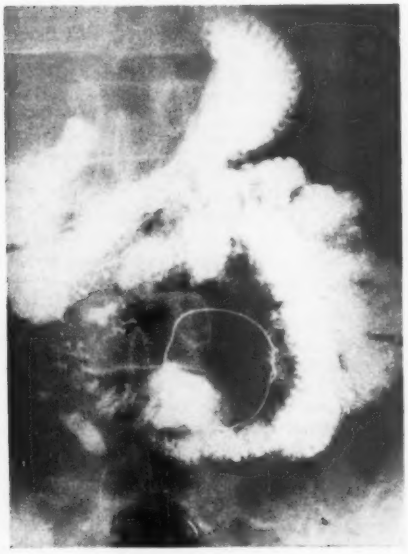

FIG. 6 (*Case XXVII*).—A man of 33 years with a large neoplastic ulcer of the jejunum.

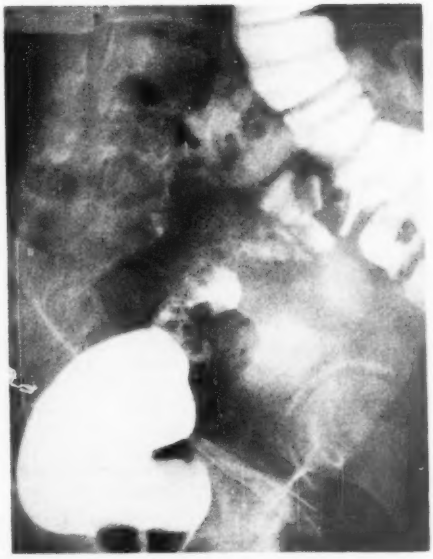

FIG. 8 (*Case XXXII*).—Barium enema in a woman of 62 years with Crohn's disease of ileum and colon showing the presence of a sigmoid-vesical fistula.

Case XXIV.—The lower ileum was grossly constricted in a woman of 55 years but a Meckel's diverticulum was by-passed by the disease. The gross constriction extended for about 1 ft. (30 cm.) but at laparotomy œdematous changes were present in the bowel wall for at least 3 ft. (90 cm.) higher up the ileum.

Case XXV.—Barium meal examination in a man of 25 years showed lower ileal constriction with internal fistulæ to the sigmoid colon which were later confirmed at laparotomy.

It is rare to find very gross ileal distension in an obstructive lesion but Case XXVI is an example.

Case XXVI.—A man of 55 had had resection of his cæcum and ascending colon for tuberculous disease nine years ago. He now complained of diarrhœa, lost of weight and skin pigmentation. Plain films of the abdomen showed gross distension of the small bowel with fluid levels but gas was present in the colon. A barium meal examination showed enormous dilatation of the lower ileum with constriction at the site of the anastomosis. Histology of the excised stricture and dilated ileum was indeterminate and might have been due either to Crohn's disease or to tuberculosis; no tubercle bacilli were found.

Frank melæna in the absence of radiological evidence of œsophageal, gastric or duodenal abnormalities when combined with negative gastroscopic findings should always raise a suspicion of small bowel neoplasm.

Case XXVII.—A 33-year-old coal-carter complained of lassitude, pallor and dark motions for a year. A central abdominal mass was palpable. Barium meal examination showed gross irregularity in a loop of upper jejunum which was displaced forwards (Fig. 6). Laparotomy by Mr. J. W. P. Gummer showed a large ulcerating jejunal carcinoma with glandular mesenteric involvement.

Case XXVIII.—A very fat woman of 76 had had melæna off and on for six years. Recent regurgitation and heartburn suggested the presence of a hiatus hernia. Barium meal examination showed some duodenal dilatation and an annular constriction in the uppermost jejunal loop. This carcinoma of the jejunum was also excised by Mr. Gummer.

Miscellaneous Cases

Cases XXIX and XXX.—A man of 29 and a woman of 23 examined by barium meal showed the presence of numerous roundworms in the small bowel.

Case XXXI.—A man of 83 succumbed to a urinary infection. The calcified opacities shown in the plain film of his abdomen are fæcoliths in a Meckel's diverticulum (Fig. 7). A similar case has been reported by Boldero (1958).

Case XXXII.—A woman of 62, who was known to have Crohn's disease for many years, complained of pneumaturia. Barium meal examination showed gross ileal involvement and a barium enema showed a vesico-colic fistula (Fig. 8).

Case XXXIII.—A child of 7 months presented with a huge hard central abdominal mass. A plain film of her abdomen showed virtually no gas in the intestine. Barium meal examination showed that the mass was displacing the whole of the small bowel upwards and backwards and one loop of jejunum was markedly stretched out round a portion of it (Fig. 9). Laparotomy by Mr. T. G. I. James revealed a mesenteric fibroma which was removed satisfactorily. Five-year follow up has revealed no untoward development.

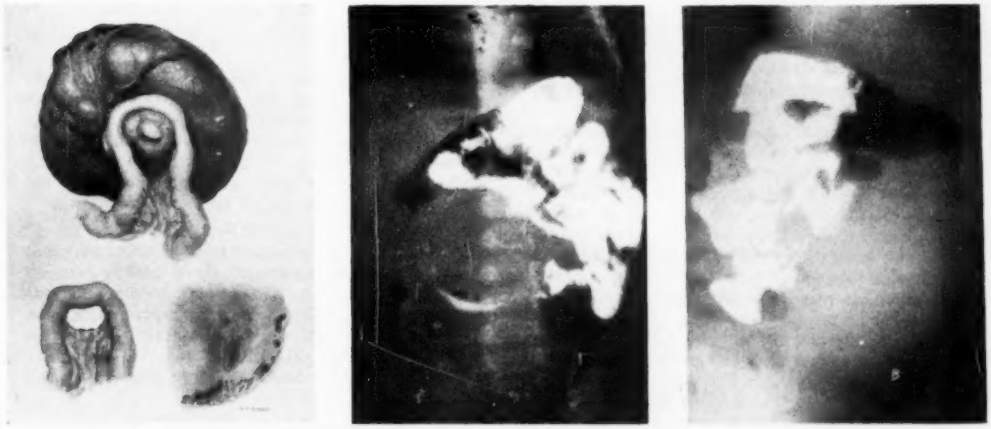

Fig. 9 (*Case XXXIII*).—A child of 7 months with a large mesenteric fibroma which has button-holed one arcade and stretched out the corresponding loop of small bowel.

Case XXXIV.—A case of "organic hysteria" recorded by courtesy of Dr. Richard Asher. A woman of 44 literally starved herself to death over a period of five years during which she lived in a dirty and neglected state in one room. Her weight three months before death was 4½ st. and this included a good deal of famine œdema. Radiographs of her dorso-lumbar spine showed extreme osteoporosis and a senile type of kyphosis. At autopsy no organic abnormality was found apart from the extreme emaciation. Clearly her small bowel suffered from having nothing to do and so did she.

REFERENCES

BOLDERO, J. L. (1958) *J. Fac. Radiol.*, **9,** 157.
SCHATSZKI, R. (1943) *Amer. J. Roentgenol.*, **50,** 743.
SCOTT, M. G. (1950) *Brit. J. Radiol.*, **23,** 575.
SPIRO, M. (1954) *Brit. J. Radiol.*, **27,** 251.

DISCUSSION

Dr. J. W. Paulley: I should like to thank Dr. Shiner for her kind references to my earlier work on jejunal biopsy at laparotomy (Paulley, 1952, 1954). But Knud Faber (1904) and Justi (1913) first discovered these histological abnormalities, and Thin (1890) and Manson-Bahr (1912–14, 1924) did so in tropical sprue. These observations were contradicted by Thaysen (1932) for the non-tropical disease, and by Fairley (1936) for sprue. For many years afterwards, and until we began to examine biopsy material, it was believed that there was no specific histological lesion in these disorders.

My own recent study (Paulley, 1958) of 200 specimens of jejunal biopsies taken at the operation of gastrectomy has given me an idea of the normal. It is against this background that I suggest there may be some mucosal abnormality in post-gastrectomy steatorrhœa, and that at present it is important to keep an open mind on this matter. It is equally important to do so on the question of whether the mucosal abnormality in idiopathic steatorrhœa is always irreversible as has been suggested here and in the U.S.A. It is far too early on the limited evidence available for anyone to be dogmatic on these points, and premature attempts to do so may mislead investigators everywhere.

The abnormality I have found in post-gastrectomy steatorrhœa is not of the same degree as that found in idiopathic steatorrhœa. It is most commonly a true atrophy with widely spaced, irregular-shaped, villi with crenated borders, and pointed tips resembling Christmas trees. The glandular layer is shallow, and cellular infiltration variable in amount. I have some evidence that the severest cases of post-gastrectomy steatorrhœa may be latent examples of idiopathic steatorrhœa prior to operation.

Concerning my second point, I have a tube biopsy of an adult cœliac taken two and a quarter years after full remission on gluten-free diet, vitamins and iron. This section has been passed by many people as normal; in my view it is not normal, but the abnormality is not serious.

(Slides were shown to illustrate these points.)

REFERENCES

FABER, K. (1904) *Arch. VerdauKr.*, **10,** 333.
FAIRLEY, N. H. (1936) *Trans. R. Soc. trop. Med. Hyg.*, **30,** 9.
JUSTI, K. (1913) *Arch. Schiffs- u. Tropenhyg.*, **17,** 505.
MANSON-BAHR, P. (1912–1914) Report on Researches on Sprue in Ceylon. Cambridge.
—— (1924) *Lancet*, i, 1148.
PAULLEY, J. W. (1952) *Trans. R. Soc. trop. Med. Hyg.*, **46,** 594.
—— (1954) *Brit. med. J.*, ii, 1318.
—— (1958) Proceedings World Congress of Gastroenterology. Washington. In press.
THAYSEN, T. E. H. (1932) Non-tropical Sprue. London.
THIN, G. (1890) *Brit. med. J.*, i, 1357.

Mr. Irvine Smith: Dr. Rowland's decision to exclude discussion of motility from his carefully planned review of the clinical aspects of small bowel function seems justified because we still know so little on this subject. However, study of motility in the œsophagus, cardia, pylorus, colon and anal canal has already proved helpful to the clinician as well as interesting to the physiologist. Unfortunately small bowel motility has remained obscure because of difficult access, inadequate apparatus and confusing records.

I was able to study motility in the intact small intestines of unanæsthetized dogs in the Mayo Clinic Laboratories using serial balloons only 1 cm. in diameter and 1·5 cm. apart, and open-ended tubes. I found three distinct types of waves:

(1) *The small waves* were present throughout most of each experiment. The intraluminal pressure usually rose by 10 to 30 cm. H_2O. In the jejunum these waves were very regular (18 to 21 waves/min.) and proceeded 3 to 9 cm. or farther down the bowel at speeds varying from 2 to 15 cm./sec., apparently propelling intestinal contents forwards. In the ileum the same waves were slower, inco-ordinated, less regular, and apparently well adapted for mixing bowel contents.

(2) *The compound waves* were groups of small waves which raised the bowel tone for periods varying from 30 seconds to 15 minutes. They were propagated quite slowly (2–8 cm./min.). Other workers have already shown that these waves appear after stretching or other local stimulation of the bowel, and that they propel boli slowly forwards.

(3) *The peristaltic rush* ("The Post Mortem Wave" of Mall, 1896) was produced by injection of morphia, but was not seen spontaneously in healthy animals. It is characterized by its very high amplitude (sometimes exceeding 300 cm. H_2O), its rapid propagation (2–10 cm./sec.) and the wave of relaxation which invariably precedes it. Before dogs vomited (after morphia) this wave passed along the jejunum *towards* the duodenum.

Although we still know relatively little about the behaviour of small bowel contractions, I believe that future research in this field will prove valuable

to clinicians and physiologists alike, as has already been the case in other parts of the alimentary canal.

REFERENCE

MALL, F. (1896) *Johns Hopk. Hosp. Rep.*, **1**, 37.

Dr. B. C. Morson: I should like to comment on the histological changes seen in the small intestine of patients with steatorrhœa. Such mild, chronic inflammatory changes with atrophy are found in both the small and large intestine when the bowel has been defunctioned or when there has been stasis of the intestinal contents. I wonder whether these histological changes in the mucosa are the primary lesion and whether the atrophic process also involves the muscle layers and the nervous or vascular tissue in the intestinal wall.

Dr. T. Csato reported on a study still in progress on the effect of oral glucose on gastric and small bowel motility and its relation to the glucose tolerance curve.

Standard records are: glucose tolerance curve, radiograph (barium), and radiograph (barium plus glucose).

The investigation comprised 24 controls and 70 patients who exhibited intermittent and incomplete symptoms of non-tropical sprue.

The second group, 5–10 sec. after drinking 50 grams glucose in 4 oz. tapwater, showed rapid peristalsis and dilatation in the second and third part of the duodenum, elicited by glucose in the stomach (glucose-water was still seen floating on the barium). This was followed 30–60 sec. later by one or two deep, slow waves passing from the antrum towards the closed pylorus. As the second wave subsided the pyloric antrum was dilated and of deep hour-glass shape.

The *proximal* jejunum reflects the duodenal response with intermittent departures, sudden arrests, and varying degrees of distension; and the meal progressed, in some cases quickly filling the *distal* jejunum. In the majority the head of the meal halted at the end of the first jejunal loop from several minutes up to an hour. *The motility changes after glucose showed that the bowel acted from the pylorus to the first loop of the jejunum as an independent unit.* In some instances glucose had dramatic effect arresting hyperperistalsis in the entire jejunum.

The mean maximum rise of the sugar tolerance curve in this group was 18 mg.%. Some "curves" were straight horizontals, a few were inverted and the interference with peristalsis by glucose was directly related to its diminished absorption. Glucose tolerance tests without barium gave identical results.

In the 24 controls motility was not altered by glucose and the sugar tolerance curves were within normal limits.

Dr. M. Shiner: I am grateful to Dr. Paulley for his remarks, especially as his studies form the only means of comparison with those of Dr. I. Doniach and myself on the histopathology of the small intestinal mucosa. I agree with him that we should be careful about minor villous variations. At the present stage of our knowledge it is better to recognize the two extreme mucosal appearances, normal and partial or almost total villous atrophy, and to keep an open mind on the various deviations from the normal villi.

The method by which mucosal specimens are obtained differs in Dr. Paulley's and my own case. Both methods probably inflict some damage to the very fragile villous tissues. It is not impossible that this results in certain irregularities of the villi as observed by Dr. Paulley and ourselves.

Replying to Dr. Morson's comments, I do not really think that a "defunctioned" bowel can be responsible for the atrophic appearances of the villi and villous surface cells or the thickening of the mucosal layer with hyperplasia of the glands of Lieberkühn, as seen in idiopathic steatorrhœa. It must be remembered that distinct cellular changes occur along with flattening of villi. Radiologically, the small bowel is usually dilated in idiopathic steatorrhœa and this may be due to lack of tone in the muscular coats or some degeneration within the muscular layers. It is noteworthy that no abnormalities have been seen in the muscularis mucosæ in our cases.

SECTION II

Chairman—HAROLD EDWARDS, C.B.E., F.R.C.S.

Small Intestinal Polyposis

By T. L. DORMANDY, F.R.C.S.Ed.
London

FAMILIAL polyposis of the small intestine is probably no less common than familial polyposis of the colon; but only in recent years—as part of the Peutz-Jeghers syndrome—has it achieved comparable recognition. The Peutz-Jeghers syndrome consists of polyposis of the gastro-intestinal tract and melanin pigmentation of the buccal mucosa, the face, and other parts of the skin (Peutz, 1921; Jeghers *et al.*, 1949).

The polyps of small intestinal polyposis, like those of familial polyposis of the colon, are true adenomas. In the small intestine they seem to arise from primitive adenomatous vesicles which lie embedded in the bowel-wall. Hundreds or thousands are usually grouped together over varying lengths of gut with normal segments intervening: though only a small proportion of them (sometimes only one or two) grow into naked-eye polyps, these microscopic adenomas are not above suspicion as a cause of symptoms and signs. The origin of the polyps from the deeper layers of the gut-wall probably accounts for the many histological diagnoses of malignancy. Clinically, despite their undifferentiated appearance and apparent invasiveness, small intestinal polyps do not become malignant (Dormandy and Edwards, 1956). This may seem remarkable considering that similar polyps in the colon—even in the same patient, and even though transmitted by the same gene—almost invariably become cancerous if left for long enough (*Lancet*, 1957; Dukes, 1958; Thompson, 1958).

Gastro-intestinal polyposis—of which small intestinal polyposis is the most constant feature—is usually associated with melanin-spots on the buccal mucosa, the lips, and the face; less commonly on the fingers, the palms, and the soles of the feet; and very occasionally in other parts of the body. Both traits are transmitted as mendelian dominant characteristics; and it is rare for one or the other not to declare itself. The constant genetic association of two such strikingly different abnormalities is not unique: the syndromes of polycystic kidneys and cerebral aneurysms (Poutasse *et al.*, 1954), of neuro-fibromatosis and café-au-lait patches on the skin, or the Lawrence-Moon-Biedl syndrome are some other examples. True pleotropism—that is multiple primary actions of a single gene—is no longer a favoured explanation. It seems more likely that the peccant gene has but a single action; but this may be many steps removed from any clinically obvious manifestations (McKusick, 1957). The consequences of a goat introduced on to a previously goatless oceanic island would be widespread and profound; but soon it would be difficult to sleuth out the primary cause of all the complex though interrelated changes in the island's physiognomy, fauna and flora (Stern, 1949). The difficulties would be especially great for one who might be as unfamiliar with the island's original character as we are with the normal genetic milieu in which the mutant gene must express itself. The influence of this milieu is shown by the effect of the patient's normal colouring on the abnormal pigmentation. The first observers of the Peutz-Jeghers syndrome mentioned dark hair and dark complexion as an essential part of the inherited abnormality (Jeghers *et al.*, 1949; Tanner, 1951). In fact the syndrome does affect fair-haired people and families; but the spots in them are far less impressive.

Many lesser abnormalities—some of them congenital or familial—may be associated with the polyposis and the pigmentation. Though co-incidence—as well as a general lowering of the threshold of the phenotypic expression—is probably responsible for most, one of them may hold the key to their elusive common genetic denominator. Three members of the family originally described by Peutz, and a few cases recorded since, had bladder and nasal as well as gastro-intestinal polyps: and at least one patient also had bronchial adenomatosis (Peutz, 1921; Hafter, 1954; Dormandy, 1957). It is conceivable that the defective gene causes a temporary but widespread dislocation at a vital stage in the embryonic development of these mucous membranes. Like familial polyposis of the colon (Gardner and Richards, 1953; Oldfield, 1954; Weiner and Cooper, 1955; Shephard, 1958), small intestinal polyposis is occasionally associated with more-or-less bizarre skeletal and cutaneous malformations—multiple exostoses, scoliosis, sebaceous cysts, vitiligo, and multiple fibromas (Devic and Bussy, 1912; Cabot, 1935; Tanner, 1951; Zanca, 1956). The commonest

is clubbing of the fingers and toes: its severity, like the extent of the pigmentation, is unrelated to the severity of the gastro-intestinal symptoms (Ravitch, 1948; Jeghers *et al.*, 1949; Dormandy, 1958). Of various visceral abnormalities I would mention small intestinal and duodenal diverticulosis (Dormandy, 1957): this makes the already difficult radiological diagnosis of polyps virtually impossible. Mental and physical retardation figured prominently in early case-reports (Niemack, 1902; Mandillon and Georget, 1935; Hillemand *et al.*, 1952); but for some of these cases prolonged blood loss and malabsorption may have been responsible. On the other hand, several members of two recently discovered families with the Peutz-Jeghers syndrome have had sporadic congenital goitres, and in one family a history of cretinism is coming to light. This is a very tenuous link with genetic enzyme deficiencies; but it is possible that eventually both polyps and pigmentation will be capable of being expressed in relatively simple biochemical terms.

Turning from the brink of fiction to clinical reality, the diagnosis of small intestinal polyposis is relatively simple when the melanin pigmentation is present, remembered, and looked for. I would merely recall that the cutaneous spots tend to become sparser and lighter after puberty and that they may be absent from all sites except the inside of the lips and cheeks. To a few patients they are a considerable affliction: "dirty" lips can make a child's life at school very miserable, and at least one woman chose to undergo repeated plastic operations to get rid of them. On the whole, however, the spots need to be remembered rather than eradicated.

Even in patients with immaculate lips and cheeks, small intestinal polyposis still presents a very characteristic clinical picture: these patients suffer from transient and self-reducing, but often multiple and almost always recurrent small intestinal intussusceptions. These give rise to attacks of brief but severe abdominal colic: and during the attacks— which are often accompanied by loud borborygmi—the patients may have a sensation of a lump or lumps rolling about inside them. Indeed, many say that they can palpate the lumps moving. The attacks tend to end as abruptly as they began, not infrequently in response to some trick movement or pressure on the abdomen; but they may recur for months or years either at irregular intervals or striking with agonizing regularity every morning after the patient gets out of bed or after the main meal of the day. "Nerves" is still the commonest misdiagnosis, and it is not difficult to see why: the fact that the pain tends to be localized to different parts of the abdomen on different days, the patient's insistence on feeling noisy lumps rolling about during attacks, the lack of abnormal physical signs between attacks, and the usually fair general health after a history of many years of suffering, all conspire to mislead. Even in hospital the patient may be rolling about in agony one minute with an easily palpable tender mass or several masses in his abdomen; and the next minute he may be perfectly free from symptoms and lumps.

I mentioned that the intussusceptions are not necessarily associated with large polyps: occasionally at operation one part of the gastro-intestinal tract may be riddled with them but none is found in the intussuscepted segments (Dubourg *et al.*, 1952; River *et al.*, 1956; Staley and Schwartz, 1957). Similarly, the occasional patient with signs of intestinal malabsorption may have only a few polyps. It seems not unreasonable to assume that aggregations of microscopic adenomas, which can disrupt normal motility and precipitate intussusceptions, can also interfere with absorptive function.

REFERENCES

Cabot, R. C. (1935) *New Engl. J. Med.*, **212,** 263.

Devic, T., and Bussy, F. (1912) *Arch. Mal. Appar. dig.*, **6,** 278.

Dormandy, T. L. (1957) *New Engl. J. Med.*, **256,** 1093.

—— (1958) In: Modern Trends in Gastro-Enterology (2nd ser.) Edited by F. Avery Jones. London.

——, and Edwards, J. H. (1956) *Gastroenterologia*, **86,** 456.

Dubourg, G., Dubarry, J., Carles, J., Gaillard, P., and Delbes, P. (1952) *Arch. Mal. Appar. dig.*, **41,** 540.

Dukes, C. (1958) *J. R. Coll. Surg. Edinb.*, **3,** 3.

Gardner, E. J., and Richards, R. C. (1953) *Amer. J. hum. Genet.*, **5,** 139.

Hafter, E. (1954) *Gastroenterologia*, **84,** 341.

Hillemand, P., Patel, J., Chérigié, P., Rosenstiel, R., and Manteau, P. (1952) *Pr. méd.*, **60,** 911.

Jeghers, H., McKusick, V. A., and Katz, K. H. (1949) *New Engl. J. Med.*, **241,** 933.

Lancet (1957) ii, 475.

McKusick, V. A. (1957) *Amer. J. Med.*, **22,** 676.

Mandillon, P., and Georget, M. (1935) *Rev. Chir., Paris*, **73,** 238.

Niemack, J. (1902) *Ann. Surg.*, **36,** 104.

Oldfield, M. C. (1954) *Brit. J. Surg.*, **41,** 534.

Peutz, J. C. A. (1921) *Ned. Maandschr. (Geneesk.)*, **10,** 134.

Poutasse, E. F., Gardner, W. J., and McCormack, S. J. (1954) *J. Amer. med. Ass.*, **154,** 741.

Ravitch, M. M. (1948) *Ann. Surg.*, **141,** 5.

River, T., Silverstein, J., and Tope, J. W. (1956) *Surg. Gynec. Obstet.*, **102,** 1.

Shephard, J. A. (1958) *J. R. Coll. Surg. Edinb.*, **4,** 31.

Staley, C. J., and Schwartz, H., II (1957) *Surg. Gynec. Obstet.* (Internat. Abstr.), **105,** 1.

Stern, C. (1949) In: Genetics, Paleontology and Evolution. Edited by G. L. Lepsen, E. Mayr and G. G. Simpson. Princeton.

Tanner, N. C. (1951) *Proc. R. Soc. Med.*, **44,** 405.

Thompson, H. R. (1958) *Proc. R. Soc. Med.*, **51,** 241.

Weiner, R. S., and Cooper, P. (1955) *New Engl. J. Med.*, **253,** 395.

Zanca, P. (1956) *U.S. Forces med. J.*, **7,** 1.

Carcinoid Tumours

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According to the original description (Thorson *et al.*, 1954), functioning carcinoid tumours may present the following syndrome: (1) Malignant carcinoid of the small intestine with slow progression, and metastases in the liver and the intra-abdominal organs: the tumour secretes 5-hydroxytryptamine (5-HT) into the circulation and it has now been established that almost all the features of the syndrome are the result of its actions.

(2) Dependent œdema, frequent watery stools, borborygmi and abdominal pain were common symptoms.

(3) Generalized widening of the small vessels of the skin with, in some cases, telangiectases.

(4) Peculiar patchy flushing of the skin combined with pilomotor symptoms, plethoric coloration, and total or partial cyanosis in the absence of polycythæmia.

(5) Pulmonary stenosis of the valvular type and tricuspid regurgitation.

(6) Attacks of bronchial asthma of a rather unusual type.

Carcinoid Syndrome

We have recently had the opportunity of investigating 8 cases of the syndrome (Table I) showing these features in whole or in part. The more severe cases showed generalized flushing of the face, neck and trunk. The vasomotor changes were sometimes spontaneous but occasionally precipitated by such stimuli as emotion (commencement of ward round), diet (tea, coffee or alcohol), pharmacological (histamine or reserpine), or mechanical (abdominal palpation or the administration of enemata). It was found impossible to influence the flushing by 5-HT antagonists such as brom-ortho-lysergic acid, or antihistamine agents.

Diarrhœa with or without abdominal colic may be one of the principal complaints of these patients (Sinclair, 1957). Borborygmi are often audible at a distance. This raises the question of "pseudo-obstruction" in the carcinoid syndrome—how colicky abdominal pain and incessant augmented bowel sounds in the presence of an abdominal mass may erroneously lead to a diagnosis of subacute obstruction of the small bowel. This may prove even more deceptive in that, at operation, the bowel may show evidence of dilatation and hypertrophy of its muscle coats without true obstruction of its intestinal lumen by the carcinoid tumour. That these effects, clinical and pathological on smooth muscle, have been provoked by 5-HT rather than by true obstruction was well demonstrated by one of our cases in which the carcinoid was almost entirely outside the wall of the bowel in the mesentery.

Asthmatic-like attacks with respiratory stridor are also the result of direct 5-HT constriction of the smooth muscle in the trachea and bronchi; difficulty may be experienced by the anæsthetist in inflating the chest to oxygenate the patient if an atack supervenes during an operation for the removal of a carcinoid.

Occasional findings are œdema, which may variously arise from cardiac failure, obstruction of veins by a large abdominal mass, and as a result

Table I.—Clinical Manifestation, Site of Tumour and Urinary Excretion of 5-Hydroxyindole Acetic Acid (5-HIAA) in 8 Cases of the Syndrome

Note that a high urinary excretion of 5-HIAA is not in every instance accompanied by severe symptoms; secondary spread (invasion locally, to glands or to the liver) had occurred in all cases. Pulmonary stenosis was proved in one case, and is clinically suspected in another.

Case	Clinical			Site	Excretion of 5-HIAA (mg./24 hr.)
	Flushing	Pulmonary stenosis	Diarrhœa		
1	−	−	±	Small bowel and liver	688 594
2	+	−	−	Ileo-cæcal and mesentery. Not liver	155
3	+	−	±	Ileum and mesentery. Not liver	65 90 84
4	+ +	+	+	Ileum, mesentery and liver	258 269
5	−	−	−	Ileo-cæcal and mesentery. Not liver	43
6	±	−	+ +	Liver and glands, recurrent after excisional operation	40
7	+ +	+ (?)	+	Ileum, mesentery	160
8	+	−	+ +	Duodenal wall, invading pancreas	82

of antidiuresis; oliguria, rarely amounting to anuria; lesions like rheumatoid arthritis affecting the smaller joints in some cases; scleroderma and a higher overall incidence of gastric and duodenal ulceration. It is surprising that few of these patients show psychological abnormalities, in spite of the important role of 5-HT in cerebral function. Perhaps this is the result of the poor penetration of 5-HT through the blood-brain barrier.

Cardiac Lesions

The development of cardiac lesions such as pulmonary stenosis and tricuspid regurgitation is an unexplained feature of the syndrome; right axis deviation may be the first abnormality seen, followed by a short systolic murmur heard best over the pulmonary area and confirmed by phonocardiography. Screening may later show avascular lung fields and straightening of the left border of the heart outline associated with enlargement of the pulmonary conus and right ventricular enlargement. Nothing further seems to be known of the origin of the endocardial lesions. Goble *et al.* (1955) reported that the concentration of 5-HT, which must be high in the portal and hepatic venous blood, remained very high in the right heart but fell to lower levels after passage of blood through the pulmonary circuit. They attributed the substantial removal of 5-HT from the blood in its passage through the lungs to the action of amine oxidase, and felt that the difference in HT concentration accounted for the higher incidence of lesions in the right side of the heart. These observations, however, have not been confirmed by Sjoerdsma *et al.* (1956, 1957) who found no difference between the 5-HT content of pulmonary artery blood and femoral artery blood.

Laboratory Studies

5-HT is eliminated from the body by oxidation to 5-hydroxyindole acetic acid (5-HIAA) through the activity of the enzyme, amine oxidase. 5-HIAA combines with α nitroso β naphthol to give a purple-coloured substance which serves as the basis for a urinary colorimetric test (Udenfriend *et al.*, 1955; Macfarlane *et al.*, 1956). All the cases examined by us were excreting vastly increased amounts of indolic derivatives (normal range 2–13 mg. per day; carcinoid tumours 20–600 mg. per day). Large numbers of indolic compounds (5-HIAA, indole acetic acid, indican, 2-amino-3-hydroxyacetophenone O-sulphate, tryptophan, probably 5-hydroxyindole acetic acid O-sulphate) were all present; in the typical case, 5-HT itself is not usually present or detectable, nor is the precursor 5-hydroxytryptophan (5-HTP).

Despite rapid conversion to 5-HIAA, a high blood level of 5-HT was found in all the secreting cases. The level in the plasma rose during a flushing attack whether spontaneously produced or by the administration of reserpine which causes a relative depletion of 5-HT in the tissues and proves useful as a provocative agent in the non-secreting cases.

Role of 5-HTP

In one exceptional case with multiple metastases, 5-HT and 5-HTP were both present in the urine in considerable amounts. This represents a valuable confirmation of the postulated route of formation of 5-HT, since in this subject's urine the precursor, active substance and breakdown product were present together, having presumably "leaked out" into the urine from a renal metastatic site. Dalgliesh and Dutton (1957) deduce that the tumour, and so presumably the normal argentaffin cells from which the tumour has arisen, must be capable of 5-hydroxylation of tryptophan. It follows that the major function of the argentaffin cells may not be the local release of 5-HT but the manufacture of its precursor, 5-HTP for circulation to various other cells which decarboxylate it and turn it into the active hormone locally. This would account for the fact that though 5-HT is produced by different kinds of cells, no other kind of tumour produces excess of it.

An atypical case, such as this one secreting 5-HTP, may owe its unusual features to its unusual cellular composition; it has been suggested that some tumours are argyrophil rather than argentaffin in type (Sandler and Snow, 1958). This unusual type of carcinoid may have osseous metastases, a brick-red flush, 5-HTP and 5-HT in the urine, and a high urinary histamine. The flushing attacks may be the result of histamine liberation in the tissues since they could be attenuated by treatment with an antihistamine; Feldberg and Smith (1953) showed that 5-HT could release histamine in certain species and this may modify the syndrome significantly.

Metabolic Aspects

The classical carcinoid syndrome may be modified in yet another way. It is now well established (Sjoerdsma *et al.*, 1956; Smith *et al.*, 1957) that the source of 5-HT is the dietary tryptophan. In some cases a very large proportion of the normal intake of tryptophan is diverted to meet the requirement of the tumour in the formation of 5-HT and this, combined with the diarrhœa often present, leads to considerable risk of tryptophan deficiency. Since tryptophan is the precursor of nicotinic acid,

this becomes apparent as nicotinic acid deficiency or pellagra. It would appear that the tumour has a basic rate of production of 5-HT. Increases in available tryptophan on a high-protein diet may increase the rate of production slightly but not in proportion to the increased availability. The tumour draws, however, on all available circulating plasma tryptophan till 5-HT production is satisfied. Sjoerdsma *et al.* (1957) have examined some of these points in detail; they found that the plasma tryptophan was low in carcinoids, even on a tryptophan intake exceeding 1,000 mg. and at a time when there had been no diarrhœa or change in weight. They also found that the urinary excretion of N′-methyl nicotinamide was lowest in the cases with the highest urinary hydroxyindole excretion. Studies with radioactive 5-HTP enabled them to estimate that some of those cases had a tumour pool of over 2,000 mg. of 5-HT, which is all the more striking when one recollects that serious pharmacological changes may follow the systemic injection of 1–2 mg.

Treatment

Surgical measures may be employed in treatment and the anæsthetist should be forewarned of possible complications such as bronchospasm and hypotension, both of which may follow handling of the tumour. Surgical removal of the tumour (most functioning carcinoids are situated in the terminal ileum) may not be possible because of local fixity, and an ileo-transverse colostomy may have to be done as a palliative procedure. Any reduction in the size of the tumour, by local resection of secondaries or hepatic lobectomy, may help to reduce the 5-HT effects.

Most cases of the syndrome, however, are patients who have had a laparotomy three to five years previously and are treated by general medical measures to minimize the flushing, the diarrhœa and the bronchospasm. Chlorpromazine, brom-ortho-lysergic acid diethylamide (B.O.L.) and 1-benzyl-2, 5-dimethyl serotonin hydrochloride (B.A.S.) are specific antagonists which should be given a clinical trial in each case. Probanthine may help to lessen the diarrhœa and aminophylline the respiratory distress. Phentolamine, dibenamine and ergotamine tartrate may also be tried. Pellagra and other vitamin deficiencies should be avoided by the administration of nicotinic acid by the parenteral route. If the plasma proteins are low, general improvement may follow blood transfusion. Little improvement follows restriction of protein intake since the tumour forms an unvarying amount of 5-HT. Occasionally the consumption of tea, coffee and fat may trigger the flushing attacks and these may have to be omitted from the diet. Alcohol almost always provokes intense flushing.

Although the clinical manifestations of the syndrome have been recounted in some detail, only a few cases show all of those features. Though a rarity, the syndrome is an important one since the recognition of more cases will afford opportunity for the study of the physiological role of 5-HT—one should remember how much the study of another rarity, Addison's disease, contributed to the elucidation of the function of the hormones of the adrenal cortex.

Acknowledgments

Part of this work was done with Drs. C. E. Dalgliesh and R. W. Dutton of the Postgraduate Medical School, London, with Dr. Lloyd Nyhus of Seattle, and with Drs. P. S. Macfarlane and B. Lennox of the Department of Pathology, Western Infirmary, Glasgow.

References

Dalgliesh, C. E., and Dutton, R. W. (1957) *Brit. J. Cancer*, **11**, 296.
Feldberg, W., and Smith, A. N. (1953) *Brit. J. Pharmacol.*, **8**, 406.
Goble, A. J., Hay, D. R., and Sandler, M. (1955) *Lancet*, ii, 1016.
Macfarlane, P. S., Dalgliesh, C. E., Dutton, R. W., Nyhus, L. M., and Smith, A. N. (1956) *Scot. med. J.*, **1**, 148.
Sandler, M., and Snow, P. J. D. (1958) *Lancet*, i, 137.
Sinclair, I. S. R. (1957) *Proc. R. Soc. Med.*, **50**, 447.
Sjoerdsma, A., Weissbach, H., and Udenfriend, S. (1956) *Amer. J. Med.*, **20**, 520.
——, ——, Terry, L. L., and Udenfriend, S. (1957) *Amer. J. Med.*, **23**, 5.
Smith, A. N., Nyhus, L. M., Dalgliesh, C. E., Dutton, R. W., Lennox, B., and Macfarlane, P. S. (1957) *Scot. med. J.*, **2**, 24.
Thorson, A., Björck, G., Björkman, G., and Waldenström, J. (1954) *Amer. Heart J.*, **47**, 795.
Udenfriend, S., Titus, E., and Weissbach, H. (1955) *J. biol. Chem.*, **216**, 499.

Discussion

Dr. M. Sandler: Mr. Smith mentioned the group of atypical carcinoid tumours which Snow and I demarcated recently (Sandler and Snow, 1958). These cases may be distinguished from the main group by a bright red, long-lasting flush, atypical histological appearance, osseous metastases and excess urinary excretion of 5-hydroxytryptophan, 5-hydroxytryptamine and histamine. As indole partition studies on urine obtained at bilateral ureteric catheterization ruled out the possibility of renal metastases in our patient, we consider that the unusual biochemical features derive from the secretion of 5-hydroxytryptophan by tumour tissue. (This has yet to be confirmed by direct observation.) Decarboxylation of this amino acid at sites other than the tumour would then enable a higher local concentration of 5-hydroxytryptamine to exert its

weak histamine liberator action (Feldberg and Smith, 1953). Direct renal decarboxylation would be responsible for the high urinary content of 5-hydroxytryptamine and any unchanged 5-hydroxytryptophan would spill over into the urine.

One of the case reports which we culled from the literature (Waldenström *et al.*, 1956) did not state whether 5-hydroxytryptophan was present in the patient's urine or not. However, it has since been detected not only in this patient but in another similar patient studied by these Swedish workers (Pernow, 1958).

Dr. H. G. Close and I have lately had the chance to investigate a further patient belonging to this atypical group (unpublished). We considered her to be an extremely suitable subject on whom to assess any *in vivo* inhibitory action of phenylacetic acid on 5-hydroxytryptophan decarboxylase. Davison and I had previously shown that this aromatic acid metabolite of phenylalanine had an *in vitro* inhibitory action on this enzyme (Davison and Sandler, 1958). After phenylacetic acid administration, not only was there a decrease in urinary 5-hydroxytryptamine and 5-hydroxyindole acetic acid, but this decrease was proportionately greater for 5-hydroxytryptamine. Because of relatively high renal blood flow, we consider that this was due to higher concentrations of phenylacetic acid exerting a greater inhibitory action on renal decarboxylase. Support is therefore provided for the hypothesis of direct renal decarboxylation of 5-hydroxytryptophan being responsible for increased 5-hydroxytryptamine output in the atypical carcinoid syndrome.

REFERENCES

Davison, A. N., and Sandler, M. (1958) *Nature, Lond.*, **181,** 186.

Feldberg, W., and Smith, A. N. (1953) *Brit. J. Pharmacol.*, **8,** 406.

Pernow, B. (1958) Personal communication.

Sandler, M., and Snow, P. J. D. (1958) *Lancet*, i, 137.

Waldenström, J., Pernow, B., and Silwer, H. (1956) *Acta med. scand.*, **156,** 73.

Dr. B. C. Morson: I would like to question Dr. Dormandy on the malignancy of these Peutz-Jeghers polyps. He stated that the small intestinal type of polyp was not pre-cancerous, but thought the colonic type might be. Mr. Henry Thompson recently sent me polyps of the small and large intestine from a patient with the Peutz-Jeghers syndrome, and histologically the colonic polyp was not an adenoma; it was quite different from the adenoma found in familial polyposis of the colon and rectum which Dr. C. E. Dukes has shown to be quite definitely precancerous. In my opinion the polyps, both of the small intestine and colon, found in the Peutz-Jeghers syndrome suggest a congenital type of tumour or hamartoma.

Mr. H. R. I. Wolfe: I should like to ask Mr. Smith two questions about carcinoid tumours. They relate to a patient who was under our care during the last three years of his illness. He had severe oliguria associated with œdema which was sometimes widespread, sometimes localized and not always in dependent parts of the body. On occasions it was entirely confined to the thighs. Investigations by Professor C. E. Dent revealed that the patient was unable to excrete sodium under any normal circumstances, the twenty-four-hour output averaging 1 mEq. The only way to clear his œdema was by mersalyl injections and on two occasions when mersalyl was given the output of sodium immediately increased to 300 and 600 mEq. in twenty-four hours falling again within two days to the control level. Is sodium retention a feature of carcinoid tumours?

Towards the end of the illness the possibility of surgical alleviation of the severely crippled heart was considered but because the exact cardiac lesion was unknown the idea was abandoned. At autopsy it was found that there was gross endocarditis with incompetence of the tricuspid valve, and early pulmonary stenosis with thickening and rolling of the edges of two of the valve cusps. There was a small patent foramen ovale, the edges of the mitral valve showed early thickening and there was white capping of the papillary muscles. This case is unusual in that there was a small patent foramen ovale. What I would like to know is the exact nature of the cardiac lesion on the right side of the heart in cases with metastasizing carcinoid tumours and are these patients candidates for cardiac surgery.

Dr. Dormandy, in reply: In answer to the question whether adenomatous small intestinal polyps ever become malignant, I would say that following up all available patients who had been previously reported as cases of malignant polyps, I found that over periods of many years none proved clinically malignant. Of the 23 cases I have investigated personally, malignancy had been diagnosed in 5 more than ten years before they came under my observation. 2 eventually died of cancer of the colon and rectum respectively, but none developed small intestinal cancer clinically or had malignant small intestinal polyps at necropsy. There has been no case to my knowledge in which distant or lymph-node deposits have been found secondary to malignant small intestinal polyps, though there have been many cases of abdominal carcinomatosis. This leads to the second question—whether the large intestinal polyps of these patients are less liable to malignant degeneration than ordinary large intestinal polyps. It seems to me that carcinoma of the colon and rectum crops up with extraordinary frequency in families afflicted with the Peutz-Jeghers syndrome; 3 of the patients I have seen personally, died of malignant polyps in their large intestine. When patients with known small intestinal polyposis eventually present with abdominal carcinomatosis, it is often assumed that one of their small intestinal polyps has turned malignant. In all such cases that I know of, post-mortem examination revealed the true primary to be not in the small intestine, but in the colon, rectum, or, occasionally, stomach.

Mr. Adam Smith, also in reply: With regard to Dr. Sandler's remarks, one of our cases belonged to the atypical group described by him and the Swedish workers; the patient had a bright red flushing appearance, secreted 5-HT, 5-HTP and histamine,

and had osseous metastases. The histology of the tumour was that of a non-argentaffin carcinoid. Many patients with these tumours excrete excessive amounts of uropepsinogen (they have a high incidence of duodenal ulcers), but we have found that their acid secretion varies; perhaps the acid estimation is affected by the strong motor contractions of the stomach leading to rapid emptying. With regard to the question of œdema, 5-HT has been shown by Hulet and Perera (1956) to cause sodium retention. Most often the cardiac condition seems to explain the occurrence of œdema. I think it unlikely that many patients will have cardiac surgery for pulmonary stenosis, since it tends to develop late in the disease.

REFERENCE

HULET, W. H., and PERERA, G. A. (1956) *Proc. Soc. exp. Biol. N.Y.*, **91**, 512.

"Blind Loop" Syndrome

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THE term "blind loop" is an unsatisfactory descriptive title which may be extended to cover a number of apparently diverse intestinal conditions, such as massive diverticulosis and intestinal stricture, all of which may present with a similar clinical picture of malnutrition, anæmia, steatorrhœa, &c.

Historically there was early surgical recognition of the complications of side-to-side anastomosis with subsequent pouch formation (Cannon and Murphy, 1906) and possible ulceration and perforation. There followed the observation by Meulengracht (1929) that the clinical picture of pernicious anæmia might be associated with certain intestinal abnormalities, in particular benign strictures. While it is no longer possible to accept all these early cases of pernicious anæmia as due to intestinal strictures, his paper undoubtedly stimulated work on the relation of anæmia to intestinal function.

In the early accounts the concept of intestinal auto-intoxication was predominant and, as early as 1920, Seyderhelm (1922) treated pernicious anæmia with ileostomy on the theory that bacterial poisoning might be responsible. In 2 out of 5 patients so treated he obtained a remission, with great improvement in the blood picture and gain in weight. A relapse which ended in death occurred following the closure of the ileostomy. The failure of this treatment in another patient was ascribed to the continuation of infection in the small intestine. These results were confirmed elsewhere (Dixon *et al.*, 1925).

In 1924, Seyderhelm and others were able to produce artificially a hyperchromic anæmia in a dog with an intestinal stricture, and related this anæmia, not to the degree of narrowing produced, but to the infection of the intestinal canal above the stricture which followed. Where this infection did not occur, no anæmia resulted. Other experimenters (Tönnis and Brusis, 1931, 1932) constructed in dogs blind loops which were arranged to fill by peristalsis. Anæmia was produced and extirpation of the loop greatly improved the clinical condition. Life was prolonged by the giving of liver injections. Other experiments showed that the use of intestinal antiseptics such as trichlorcresol (Horster, 1935) greatly lengthened life and prevented the onset of loss of weight and anæmia.

It should be noted that the production of blind loops does not necessarily result in anæmia. Pearce (1934) confirmed in dogs that when the segment of intestine was so arranged that it emptied, the animal remained normal, and appetite and activity was unimpaired. Only when the loop was so arranged that it filled did symptoms appear of weakness, lethargy, and loss of weight, and unless the loops were resected the animals died. He reported no significant changes in the blood.

The most recent animal work has been that of Cameron *et al.* (1949) who, after forming blind sacs under certain conditions in rats, succeeded in producing a macrocytic anæmia and confirmed and extended earlier experimental observations. They were able to prolong life and cure anæmia by using chlortetracycline and folic acid. Since some of their rats died without anæmia, they emphasized that the deficiency must be multiple. All this experimental work may be summarized by saying that the production of intestinal blind loops, sacs or strictures may profoundly affect an animal, but only when stasis has been produced; that these effects include malnutrition, anæmia, loss of weight, and may terminate in death; that the effects may be abolished by extirpation of the blind loop or sac, or the resection of the stricture; and that improvement of the animal's condition may be achieved by intestinal antiseptics, more recently by antibiotics, and also by giving folic acid, liver injections, &c.

In human pernicious anæmia, Castle's hypothesis, which fitted so many of the facts, might have been expected to destroy the theories which saw bacterial intestinal infection as in some way causative (Castle *et al.*, 1930). But Castle wrote prophetically: "Next to a defect of the original formative process within the stomach, the loss of the absorptive power of the intestinal tract, either mechanically or by way of bacterial invasion, or the destruction in the bowel of the effective principle after formation would be the most obvious ways in which a deficiency of the

final effective substance could be brought out." By 1936 Minot could write: "Occasionally, a patient with an intestinal short circuit, maintained with difficulty on liver extract administered orally, is able to maintain his blood without taking liver extract after the intestines have been returned to essentially their normal state by operative procedure." There is here the clear recognition, even if it was then not widespread, of one form of the "blind loop" syndrome.

Parallel to these clinical observations, there was another line of enquiry. By 1939, animal physiologists had pointed out that vitamin synthesis of several members of the B complex took place in the rumen of the sheep (McElroy and Goss, 1939). This was evidence that the animal's requirements of vitamins could to some extent be supplied by synthesis within the gut. These conclusions are probably true of man, so that we depend to a variable extent on the presence of bacteria in our own gut to supply our needs. There is therefore justification for thinking that the supplanting of bacteria which normally synthesize vitamins, or the growth of bacteria which themselves utilize substances required by the host, might result in a deficiency state.

There is other evidence to support this concept. The discovery that sulphonamides can alter bacterial growth in the intestine was soon followed by the observation that antibiotics can improve the utilization of food in treated animals and promote more rapid growth. These effects can be produced by a series of chemical substances which have nothing in common, apart from their antibacterial action. While there seems no clear relationship between the feeding of an antibiotic and the establishment of any particular type of bacterial growth, the empirical results are unquestioned, so that this device has proved one of the major advances in livestock husbandry. On human subjects only a few observations on the action of antibiotics in hastening growth have been carried out. There are, however, several papers which suggest that growth in children may be improved by their administration. Even in young men at the end of their growth period, significant increases in weight were observed in an antibiotic-treated group. In a more specific study, there is evidence that blood formation may be aided in patients deficient in folic acid or cobalamin by giving antibiotics which are presumed to act by promoting the bacterial synthesis of these substances (Jukes, 1955).

Evidence of a different kind is supplied by parasitology. There is no doubt that parasitized animals grow at a slower rate than parasite-free animals and that on the same food intake the weight gain is less. Why is this? There is no evidence that the parasites act by diverting calories, and the most promising hypothesis is that the parasites act by using essential trace food factors necessary for the adequate nutrition of the host.

There are therefore good grounds for thinking that malnutrition might arise from an altered flora in the intestine resulting in a deprivation of essential trace food factors. There is evidence that an altered flora may occur in blind loops or sacs of the intestine and in intestinal diverticula (Girdwood and Doig, 1957). If this general theory is accepted, then we should distinguish between those sacs or loops which, though anatomically blind, are not stagnant. For example, there is no account in the literature of the "blind loop" syndrome arising with a Meckel's diverticulum, and this is consistent with the experimental work which shows that if the sac readily empties, no untoward symptoms appear. Some writers have hinted that the afferent loop of a Polya-type anastomosis following gastrectomy in which the duodenum is closed can act as a "blind loop". It is of course blind anatomically but this particular piece of gut is extremely active, empties itself readily, and is normally washed through by pancreatic juice and bile after each meal. It is therefore not comparable to the "blind loop" formed by surgical short-circuiting of an obstruction.

If we accept as an essential condition an alteration of flora, it is somewhat difficult to see how bacteria, growing in loops or sacs and by definition out of the main intestinal current, can obtain these food factors and so deprive their host. The abnormal bacterial growth may, of course, spread throughout the bowel, but there is another explanation which deserves consideration. I refer to the concept, adopted by some parasitologists as a working hypothesis, of the exocrine-enteric circulation (Read, 1950).

If we consider the movement of substances across the intestinal wall, we all agree that a fluid secretion occurs into the gut, and that the water is absorbed elsewhere. The extent of this transfer is known to be very great. There is equally no doubt that electrolytes circulate in a similar way. No one questions that bile salts circulate with a time cycle of the order of eight to sixteen hours. Bile salts are synthesized and destroyed, but the body seems to economize by using them again and again. If this mechanism exists for bile salts, may it not occur for other substances, particularly if they play a catalytic role in biochemical reactions and so can be used repeatedly? The simplicity of the hypothesis is very attractive. There is, at any rate, a good deal of evidence to make it likely that there is such a

circulation which includes various vitamins (Read, 1950).

If this is accepted as a working hypothesis, then it is easy to see how bacteria in a stagnant loop or diverticulum can interrupt this recirculation, since these food factors may appear in all intestinal secretions. It would also explain why quite small collections of bacteria might give rise to symptoms of malnutrition, since these bacteria do not have to consume a fraction of the ingested factor, but have only to remove part of a very much smaller amount, which is being constantly recirculated. There is one other phenomenon which may be explained by this theory, and that is the reported observation (Halsted *et al.*, 1956), that the anæmia in the "blind loop" syndrome is unaffected by neomycin which is not readily absorbed, whereas it may be cured by chlortetracycline which is readily absorbed, and may therefore appear in sufficient concentration in the "blind loop".

Clinical Considerations

The frequency with which the "blind loop" syndrome follows a short-circuiting operation is unknown. Though it is probable that examples may be missed, especially if they have no severe anæmia, it seems likely that the condition is rare and this suggests that the conditions for bacterial growth in the loop, sufficient to impair nutrition, are critical and not easily attained. The symptoms of the general "blind loop" syndrome may be considered under two headings:

(1) Symptoms from the purely structural abnormality in the gut, such as the anatomical arrangement of the "blind loop", the extent of the diverticulosis, or the presence of strictures producing intestinal obstruction.

(2) Symptoms arising from intestinal dysfunction. These comprise malnutrition, which includes loss of weight, anæmia, deficiencies of essential food factors, and their resulting neuropathies. There may also be steatorrhœa, diarrhœa or colicky pain. We cannot pretend that the origin and mechanism of all these symptoms is clear.

The explanation of the anæmia, which may be due to cobalamin or folic acid deficiency, or both, has been fully reviewed and will not be discussed further (Foy and Kondi 1954; Badenoch, 1958). Deficiencies of essential food factors may lead to vitamin deficiency syndromes or to loss of weight. Steatorrhœa, which is frequently seen, is not easily explained and appears to be due to malabsorption. In the case of blind loops high up, which involve the duodenum, inadequate mixing of food with pancreatic juice is a conceivable explanation in some cases. It should also be remembered that, in any severe state of malnutrition, the pancreas may become secondarily affected and therefore the steatorrhœa becomes partly pancreatic in origin. In a case described by Brock (1939), with multiple intestinal strictures, the steatorrhœa showed only 20% splitting, suggesting a pancreatic fibrosis as responsible. Diarrhœa in a mild form is a common symptom and may be due to several causes. Occasionally it appears in a very severe form. In one patient we saw, the only complaint was of a profuse, watery diarrhœa, which came on paroxysmally, particularly at night. This description strongly recalled the diarrhœa occasionally seen with severe diabetes and which, it has been suggested, may be due to a neuropathy of the abdominal autonomic nervous system (Joslin *et al.*, 1952). His only abnormality, apart from absent ankle-jerks, was a multiple diverticulosis throughout the entire gut. There was no anæmia, and all biochemical tests were normal. In 5 cases of extensive diverticulosis, described by Badenoch *et al.* (1955), all had diarrhœa. In one of these cases there was mental change, in another there were paræsthesiæ, and in a third there was gross peripheral neuritis. The possibility that in such cases the diarrhœa is an expression of a neuropathy of the autonomic system, due to some nutritional defect, ought seriously to be considered.

Intestinal colicky pain, where obstruction is not present, may possibly be due to paroxysmal cramps of the intestine as may also occur in a diabetic neuropathy and diarrhœa.

Diagnosis

The diagnosis of a true "blind loop" or sac may be difficult if intestinal fistulous formation has occurred spontaneously. More frequently the "blind loop" follows some previous surgical operation, such as the short-circuiting of an obstruction. Provided the suspicions of the surgeon or physician are aroused when a patient shows some symptoms or signs of malnutrition following a previous abdominal operation, the diagnosis is likely to be made sooner or later. It is more easily made if the patient has a macrocytic anæmia, since an identification of its cause can now be made with considerable precision. Cases are more liable to be missed if they have no overt anæmia, or if the stools do not obviously suggest a steatorrhœa. The radiological investigation may prove difficult, or may fail, since barium will not readily enter a "blind loop", and the post-operative conditions under which "blind loops" arise make radiological interpretation difficult.

Intestinal diverticulosis may be discovered by accident radiologically; probably the majority

of cases are symptomless. It may also be found on radiological examination of a patient with malnutrition, anæmia, steatorrhœa, &c. Diverticula may fail to fill and their number and extent are always likely to be underestimated.

As a further diagnostic aid in all doubtful cases of this syndrome, an absorbable antibiotic such as chlortetracycline should be given. If clear improvement results in the blood picture or clinical state, the diagnosis is strongly supported.

Treatment

Operation may be necessary if "blind loops" are suspected, to judge the extent of intestinal diverticulosis, or, in rare instances, to resect a stricture. Before operating, it should be possible in most patients to improve their general condition and the anæmia can nearly always be ameliorated. A low-fat diet may be necessary, and mineral and vitamin deficiencies will need replacement. If a "blind loop" can be resected, and normal continuity restored, there should be a complete and dramatic recovery. If the bowel is the seat of multiple diverticulosis, this may prove at operation to be far more extensive than was anticipated, and resection may be impossible. If radical treatment is not possible, the patient can usually be greatly improved by medical measures.

If the general ætiology of all these conditions is accepted, that is, that there exists under certain conditions in the intestine an altered flora such that essential trace food factors are lost to the host, then the purely descriptive name of "blind loop" should be abandoned, to be replaced by some name which describes the functional state of privation. The concept of this privative state may then be extended. Dare we regard for instance, the fatty liver which proceeds to fibrosis, seen in some patients with severe ulcerative colitis, as, in part, a nutritional disease of the liver due to involvement of the cæcum and ascending colon, that is, that part of the gut which is said to be the main site of vitamin synthesis? Our attention was directed to this possibility when, a year ago, we saw a patient with œdema and hypoproteinæmia, who was found to have a carcinoma of the cæcum, with a fatty liver, and amblyopia. The carcinoma was successfully resected; the liver is now progressing to fibrosis. Such a possibility should receive consideration.

REFERENCES

Badenoch, J. (1958) In: Modern Trends in Gastroenterology. 2nd ser. Edited by F. Avery Jones. London; p. 231.

——, Bedford, P. D., and Evans, J. R. (1955) *Quart. J. Med.*, **24**, 321.

Brock, J. F. (1939) *Lancet*, i, 73.

Cameron, D. G., Watson, G. M., and Witts, L. J. (1949) *Blood*, **4**, 803.

Cannon, W. B., and Murphy, F. T. (1906) *Ann. Surg.*, **43**, 512.

Castle, W. B., Townsend, W. C., and Heath, C. W. (1930) *Amer. J. med. Sci.*, **180**, 305.

Dixon, C. F., Burns, J. G., and Griffin, H. Z. (1925) *J. Amer. med. Ass.*, **85**, 17.

Foy, H., and Kondi, A. (1954) *Trans. R. Soc. trop. Med. Hyg.*, **48**, 17.

Girdwood, R. H., and Doig, A. (1957) *Scot. med. J.*, **2**, 313.

Halsted, J. A., Lewis, P. M., and Gasster, M. (1956) *Amer. J. Med.*, **20**, 42.

Horster, H. (1935) *Z. ges. exp. Med.*, **95**, 514.

Joslin, E. P., Root, H. F., White, P., and Marble, A. (1952) The Treatment of Diabetes Mellitus. 9th ed. London.

Jukes, T. H. (1955) Antibiotics in Nutrition. New York.

McElroy, L. W., and Goss, H. (1939) *J. biol. Chem.*, **130**, 437.

Meulengracht, E. (1929) *Acta med. scand.*, **72**, 231.

Minot, G. R. (1936) *Amer. J. dig. Dis.*, **3**, 643.

Pearce, H. E. (1934) *Surg. Gynec. Obstet.*, **59**, 726.

Read, C. P. (1950) *Rice Inst. Pamphl.*, **37**.

Seyderhelm, R. (1922) *Ergebn. inn. Med. Kinderheilk.*, **21**, 361.

——, Lehmann, W., and Wichels, P. (1924) *Klin. Wschr.*, **3**, 1439.

Tönnis, W., and Brusis, A. (1931) *Dtsch. Z. Chir.*, **233**, 133.

——, —— (1932) *Z. ges. exp. Med.*, **84**, 728.

Massive Intestinal Resection

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The term "massive intestinal resection" has by convention come to mean the loss of more than 200 cm., or approximately 7 feet, of small bowel. The early reports were content with short-term survival and in the rivalry of the early years of the century surgeons competed in the magnitude of their resections. Of more interest to the patient is the amount of small bowel that remains and recent emphasis has shifted to the investigation of the effects of resection in survivors.

Normal Length of Small Bowel

This is extremely variable and increases with stature and in races taking a diet containing much roughage. Bryant (1924) found lengths varying between 10 ft. and 28 ft. 4 in.; Treves (1885) between 15 ft. and 33 ft., while Kallio (1932) found a mean of 22½ ft., or 675 cm., in 1,161 individuals measured *post mortem* or at operation. Alvarez (1948), however, gives a length of 8 to 10 ft. in the live state.

Measurements vary with the tone of the muscle, or the presence of the mesentery or the manner of its detachment, and should be made in the unfixed state. The length of remaining intestine cannot be deduced by a simple subtraction of the

length removed from a hypothetical normal: but when the remainder is no more than 2 or 3 ft. an approximate live measurement, either at operation or radiologically, is possible.

Reasons for Massive Resection

Removal of large lengths of intestine is not lightly undertaken but cannot be avoided when the surgeon is faced with extensive gangrene. These resections, however extensive, are always worth while since there are many who not only survive but return to a tolerable life following resection of 80% to 90% of their small bowel (West *et al.*, 1938; Todd *et al.*, 1940; Holman, 1944; Meyer, 1946; Cogswell, 1948; Althausen *et al.*, 1949; McClenahan and Fisher, 1950; Wilkie, 1950; Jackson and Linder, 1951; Berman *et al.*, 1953; Martin *et al.*, 1953; Bothe *et al.*, 1954; Trafford, 1956; Pilling and Cresson, 1957). At the same time not all have fared so well. Successful patients become notorious, but many more failures die miserably and unsung. Massive resections are uncommon and during the last ten years at St. Thomas's Hospital the records of only three resections of any length have been found and none of these exceeded 5 ft.

Analysis by Haymond (1935) of 257 patients gives the following reasons for massive resection, in the order of their frequency:

(1) Volvulus—76.	Small intestine and sigmoid (*a*) Knotenbildung (*b*) Small intestine
(2) Strangulated hernia—45.	(*a*) Inguinal (*b*) Femoral (*c*) Umbilical (*d*) Others, including hernias en-W (retrograde strangulation)
(3) Mesenteric thrombosis—34.	Arterial or venous, including embolus
(4) Female pelvic diseases—21.	(*a*) Uterine perforation (*b*) Other pelvic diseases
(5) Mesenteric disease—19.	(*a*) Primary tumours of mesentery (*b*) Mesenteric slits (*c*) Other conditions
(6) Abdominal injuries—16.	(*a*) War (*b*) Civilian
(7) Tuberculosis of intestine—16	
(8) Adhesions and bands—7.	
(9) Miscellaneous—13.	
(10) Not stated—10.	
Mortality—33·5%.	

To these must be added the following conditions, which do not appear in Haymond's classification:

(1) Crohn's disease, including stage resections.
(2) Operative hazards, e.g. pancreatectomy.
(3) Infantile atresia of bowel.
(4) Meconium ileus.
(5) Volvulus secondary to malrotation of intestine.

Amount of Small Bowel Remaining

In the early days of abdominal surgery surgeons faced with the unavoidable necessity of massive intestinal excision sought an answer to the question "How dispensable is the small bowel?" No simple answer has yet been found and the effects are very variable. Some survive, at least for a time (nine months to indefinitely) with no small bowel at all, or only a few inches (Jackson and Linder, 1951; Martin *et al.*, 1953; Brezin and Oren, 1954; Gaynor and Diefenbach, 1957), while others are severely incapacitated with resections less than massive (Posey and Bargen, 1948; Jackson and Linder, 1951). It may be, however, that surprisingly bad results after small resections are due to persisting or recurrent disease, or the formation of a blind loop or stricture in the technique of anastomosis (Jackson and Linder, 1955). In Haymond's analysis (1935) the resection of lengths greater than 13 ft. resulted in abnormal nitrogen loss in the stool, while abnormal fat excretion occurred with resections of half this extent. Haymond concluded in 1935 that "if the patient survives the operation a loss of one-third of the small bowel should permit a return to normal; resection of one-half is the upper limit of safety, while greater amounts give poorer results even though an exceptional case may be better than predicted". Since then many reports show that life is possible with as little as 18 in. of small bowel, though Haymond's conclusions still provide a good working rule (West *et al.*, 1938; Meyer, 1946; Cogswell, 1948; Althausen *et al.*, 1949; Berman *et al.*, 1950; Christensen *et al.*, 1950; Berman *et al.*, 1953; Pearce *et al.*, 1953; Bothe *et al.*, 1954; Eckstam and Barry, 1954; Jackson and Linder, 1955; Montgomery and Pincus, 1955; Schwartz *et al.*, 1955; Trafford, 1956; Pilling and Cresson, 1957).

Experimental Resection of Intestine

Experimental resection of intestine, mainly in dogs, has been carried out by many investigators since 1888 (Senn, 1888; Monari, 1896; Erlanger and Hewlett, 1901; Evans and Brenizer, 1907; Flint, 1912; Wildegans, 1925; Kunz and Molitor, 1928; Clatworthy *et al.*, 1952). They concluded in general terms that 50% of the small bowel is dispensable in the dog. Resections up to 75% were compatible with survival, though not in full health or at a normal weight. Some did well with an 80% removal, while others never truly recovered from a loss of 60% of the small bowel. There was some evidence of hypertrophy and hyperplasia of remaining intestine (Flint, 1912; Clatworthy *et al.*, 1952), though in the most massive resections this did not occur. Older dogs proved more resilient than younger ones,

but in humans (and Clatworthy's dogs) youth was an advantage (Haymond, 1935) and should be no bar to resection when indicated.

Results of Massive Resection

The patient who does not immediately succumb goes through three phases of recovery. The post-operative fluid and electrolyte crisis, associated with severe diarrhœa, which may last two or three weeks; the phase of recovery and adaptation, which may last from one to two years; and the final stage in which no further recovery takes place and in which, if recovery is incomplete, the patient learns to live with and to some extent circumvent his disability. The battle may be lost at any stage through failure of adequate compensation or intercurrent disease, to which he may be unusually prone.

In the first phase return of intestinal motility results in a profuse diarrhœa which remains one of the most distressing symptoms. It is associated with tenesmus, burning, perianal irritation and sometimes excoriation. The diarrhœa is maximal during the first two or three weeks and presents a problem of management akin to, but greater than, that of a newly formed ileostomy. The fluid electrolyte losses may be enormous, as much as a litre being passed ten or twelve times per day. The diarrhœa gradually lessens as the end of the first stage is reached.

In the second stage the emphasis shifts from fluid and electrolyte balance to nutrition. The patient rapidly loses weight and despite a large oral food intake loses much of it in the stools. The absorption of fat is most disturbed and may be almost abolished. To a lesser extent proteins are affected and carbohydrate absorption is hardly disturbed.

Vitamin deficiencies will become established in the absence of treatment. The fat-soluble vitamins A, D and K are understandably affected, though the absorption of vitamins of the B group and C is also severely restricted. Glossitis, angular stomatitis, pellagra and psychotic changes may result. Hypocalcæmia and tetany occur and, rarely, hæmorrhage due to hypoprothrombinæmia. Anæmia and hypoproteinæmia are very rare in the pure picture. The patient becomes weak and irritable and difficult to manage. He may suffer from abdominal cramps, distension and nausea.

During this stage the rate of intestinal passage gradually slows, though single evacuations may measure up to 1½ gallons (Jackson and Linder, 1955). Improvements in protein and carbohydrate absorption are demonstrable. An equilibrium is reached as compensation is established and thereafter, *in the third stage*, the problem is to find a regime which best suits the individual patient, though a relapse may at any time occur due to dietary carelessness or mental changes. It is in the behaviour of the individual towards his dietary fat, and on the ability of his physician to modify it for the better that the patient's welfare largely rests, for on this depends not only his fat intake but, more important, his protein, fat-soluble vitamins, calcium and phosphorus absorption.

Adaptation and Survival

The body must adjust itself to the impaired intake of nourishment or succumb. Weight is lost and can be supported only at a level considerably lower than before. The metabolic rate is reduced and physical activity curtailed. The absorptive capacity of the intestine is capable of improvement as time goes on, though the mechanism is uncertain. In time the rate of gastric emptying (Althausen *et al.*, 1950; Jackson and Linder, 1951) and the passage through the alimentary tract are slowed (Pilling and Cresson, 1957)—the transit of food from mouth to anus in Althausen's case (Althausen *et al.*, 1950) changing from three and a half hours on the ninth post-operative day, to eighteen hours at three weeks. Food intake is increased and eating becomes more continuous. The colon enlarges to accept the enormous volume of the fæces and probably increases its absorptive activity of carbohydrates and even of amino acids.

The effect of any given resection is unpredictable, but is better tolerated when done in stages, as sometimes happens in progressive Crohn's disease. The presence of a segment of ileum, the ileocæcal valve and as much colon as possible seems to be a decided advantage (Althausen *et al.*, 1950; Brezin and Oren, 1954; Pietz, 1956; Trafford, 1956; Pilling and Cresson, 1957).

Fat Absorption

A healthy individual normally absorbs about 95% of the ingested fat, mainly from the ileum. Absorption depends, apart from surface area, upon food arriving at the right place at the right time after contact with appropriate ferments, and there remaining for a sufficient period. If the fat is rushed through the small remnant and reaches the colon before the lipase has done its work it is already beyond the absorptive area. Such a concept has been summarized as a time-contact relationship between food, ferments and mucosa (Berman *et al.*, 1950). Splitting continues in the colon where fatty acids (especially long-chain) irritate the colonic mucosa and lower the pH of the bowel contents. As much as 97% of the ingested fat may be recovered from the stool, where approximately half of it is split.

Such figures have been obtained on a high fat intake of about 180 grams while on a lower fat intake the percentage of fat in the stool may decrease, though the amount absorbed (6·5–8 grams) does not increase (Jackson and Linder, 1951). Other writers report a loss in the fæces of 77% (Althausen *et al.*, 1949), 45% (West *et al.*, 1938; Todd *et al.*, 1940) and 20% (Christensen *et al.*, 1950), more or less according to the length of remaining bowel, though Schwartz's case (Schwartz *et al.*, 1955) absorbed 50% of ingested fat with no bowel between duodenum and transverse colon, and in two other patients fat absorption was apparently unaffected with only 3 ft. or less of remaining small bowel (Kositchek and Rabwin, 1950; McClenahan and Fisher, 1950). Absorption of vitamin A (as a measure of fat absorption) can vary between 36% and 22% of normal (Althausen *et al.*, 1950). The butter absorption test, on the other hand, shows a marked improvement with time, to almost normal performance (Althausen *et al.*, 1949; Althausen *et al.*, 1950). This may be a measure of two different mechanisms (viz. Fraser's hypothesis of dual absorption of fats) whereby the neutral fat is very much more easily handled than fatty acid (Althausen *et al.*, 1950). This observation is confirmed by others (Pearce *et al.*, 1953).

There are other factors adversely affecting the absorption of fat. The reaction of the bowel contents has been found to be at a pH of 3·5 to 6 (Jackson and Linder, 1951, 1955; Pietz, 1956); while lipase, and incidentally trypsin (Jackson and Linder, 1951), has hardly any activity at a reaction below 8 (Best and Taylor, 1955). The acidity is thought to be due to the lack of alkaline pancreatic juice and succus entericus. Pancreatic secretion has been measured and found to be reduced (Jackson and Linder, 1951) and at necropsy the pancreas is often atrophic. The flow of pancreatic juice is normally stimulated by secretin and pancreozymin (Harper and Raper, 1943) which are formed in the small bowel. Lack of these when the small bowel is missing would cause a deficient flow. The acid gastric secretion also acts as a stimulus to pancreatic activity and the frequent finding of hypochlorhydria (Jackson and Linder, 1951) might also contribute to impaired function. Thus not only is there a deficiency of pancreatic lipase, but what is available is likely to be inactivated by the low pH values.

Proteins

Not only is the absorption of protein less affected than that of fat but powers of recovery exist (Althausen *et al.*, 1950), from 17% initially to 88% eventually of average normal values, as shown by methionine tolerance test. Nevertheless, excessive nitrogen loss in the stool, mostly in the form of undigested meat fibres, is to be expected when more than 13 ft. of bowel have been lost (Haymond, 1935). Plasma proteins are maintained at a relatively normal figure and ratio until the final stages of the struggle in those who succumb to their disability. Whenever nitrogen balance studies have been carried out a positive balance is usually found (Berman *et al.*, 1950), though sometimes only when fat intake is restricted (Jackson and Linder, 1951). Increasing the fat intake reduces protein absorption. Œdema is uncommon and when it has occurred seemed to be due to causes other than hypoproteinæmia. Utilization of protein varies between 40% and 100%, according to the length of remaining bowel (West *et al.*, 1938; Todd *et al.*, 1940; Althausen *et al.*, 1950; Berman *et al.*, 1950; Pilling and Cresson, 1957). The greater ability to absorb protein (rather than fat) may be in part due to the demonstrable powers of the colon to absorb amino acids (Brezin and Oren, 1954) and the higher split products of casein hydrolysis (Short and Bywaters, 1913; Rhoads *et al.*, 1939).

Carbohydrates

The ability to absorb carbohydrate, also water, is the earliest to recover and is usually complete. Glucose absorption is the first to return, followed by that of galactose, and the absorption of methionine and glycine follow (Althausen *et al.*, 1950). Glucose is more easily handled than starch, which requires first to be hydrolysed and may well be in the colon before this is complete. The presence of so much carbohydrate in the colon in contact with the bacterial flora results in much fermentation and gas production and is thought to give rise to the abdominal cramps and bloating which these patients frequently suffer, and which can be temporarily improved by partial elimination of the flora by antibiotics (Althausen *et al.*, 1949). The stomach and duodenum are capable of some glucose absorption and the colon is thought to absorb glucose in isotonic solution at a slow rate (1/10 of that of duodenum and upper jejunum). The glucose tolerance curves are nearly always flat, which usually indicates impaired absorption, though patients deriving calories almost entirely from carbohydrates to the exclusion of fat may show increased tolerance (Jackson and Linder, 1951). If the intravenous glucose tolerance test is normal then impairment of absorption can be deduced. Excessive carbohydrate loss in the stool is not found, though this may be partly due to the utilization and destruction of carbohydrate in the colon by bacteria (Althausen *et al.*, 1949).

Vitamins

The fat-soluble vitamins (A, D, E and K) are likely to be imperfectly absorbed in the presence of steatorrhœa and the vitamin-A absorption curve is actually used as a measure of fat absorption. Plasma vitamin A and carotene have been found to be reduced (Jackson and Linder, 1955).

Vitamin B complex is poorly absorbed and vitamin B_{12} is sometimes not absorbed at all, despite normal blood pictures (Oxenhorn *et al.*, 1958; Adlersberg, 1957). This vitamin is normally absorbed from the lower ileum (Cooke *et al.*, 1957), a segment often missing after massive resection. Despite this the occurrence of macrocytic anæmia in cases of pure resection is rare, if it occurs at all.

There is also, surprisingly, extreme difficulty with vitamin-C absorption, which may show very low serum levels (Althausen *et al.*, 1949; Jackson and Linder, 1951), though reports of frank scurvy have not been found.

Minerals and Electrolytes

Iron.—Anæmia is exceptionally uncommon after massive resection when the remaining bowel is healthy and no chronic bleeding drains the body's iron reserves (Jackson and Linder, 1951, 1955). This may be explained by the modern concept of 100% iron conservation of which the body is capable (McCance and Widdowson, 1933; Whipple and Robbins, 1936). Nor has anæmia, either microcytic or macrocytic, been obtained experimentally by massive resection alone (Miller and Rhoads, 1935; Petri *et al.*, 1942; Brown, 1949), although in the presence of persistent disease or blind loops or intestinal strictures it is common.

Calcium and phosphorus.—The absorption of calcium and phosphorus seem to run roughly parallel (Todd *et al.*, 1940), the calcium loss in the stool depending directly upon the fat content and indirectly upon the fat intake (Todd *et al.*, 1940; Cogswell, 1948). Balance studies have usually shown a small negative calcium balance, but in a degree easily compensated by drawing on the body's calcium reserves. Despite the negative balance osteoporosis may not be recognizable after two or three years (Jackson and Linder, 1955; Pietz, 1956). In a few patients (19% of a series reviewed by Pietz, 1956) the calcium loss has been great enough to cause a lowered serum calcium and even tetany (West *et al.*, 1938; Cogswell, 1948; Pietz, 1956), though according to other authors this is surprisingly rare where persistent disease and blind loops are excluded (Jackson and Linder, 1955). This may be understandable if, as reported by Berman *et al.* (1950), normal fæcal values for calcium soaps can exist, despite a very high fatty acid content. Achlorhydria may aggravate the absorptive difficulty. Although calcium is for the most part normally absorbed in the duodenum and upper jejunum the presence of a segment of ileum, however small, and the ileo-cæcal valve seems to make hypocalcæmia unlikely (Pietz, 1956).

Excessive quantities of sodium and potassium are lost in the stool, sometimes amounting to ten times the normal excretion.

Other Findings

The bacteriology of the stools has not differed from normal (Jackson and Linder, 1951).

Post-mortem Findings

The liver may be normal (Jackson and Linder, 1951), though atrophy (Martin *et al.*, 1953), fibrosis (Jackson and Linder, 1955) and fatty infiltration have been recorded.

The intestinal remnant is dilated and the walls thickened by œdema and muscular hypertrophy. Sometimes a slight elongation has been found *post mortem*, but just as often no change. Hypertrophy of the mucous membrane has been described, in that the intestine is larger in calibre and there is greater redundancy of the lining (Martin *et al.*, 1953). Whether dilatation is an advantage is doubtful since it does not necessarily lead to an increase in absorptive surface, as the same amount of mucosa accommodates to the dilatation by losing some of its reduplication. Furthermore, the larger the calibre of the intestine the greater is the ratio of intestinal volume to absorptive surface. At the same time an increase in the number of mucosal cells (if it occurs) must be a gain, whatever the calibre of the gut, in which wastage of food material is inevitable.

Treatment

In the immediate post-operative phase fluid losses from all measurable sources must be charted and replaced intravenously. Serum sodium, potassium and chloride levels are checked almost daily as a guide to electrolyte losses. An adequate urinary excretion of 1–1½ litres should be maintained. All intravenous fluids should contain 5% of dextrose in solution. Intravenous fat, when available, is a useful adjunct, both as a more concentrated form of fuel and by way of supplying that food element which is most severely curtailed. Intravenous protein hydrolysate may be useful when recovery is prolonged.

Normal oral feeding is resumed as soon as possible. Food intake should be frequent and in the most massive resections almost continuous (Berman *et al.*, 1950). In this way the remaining

small bowel mucosa is used to best advantage; food passes through at an even rate and the sudden rushes and dumping of large meals, which aggravate the intestinal hurry, are avoided. The patient is gradually settled on to a diet of very low fat content, though dairy fats in cream and butter should be allowed up to the limits of tolerance (Althausen *et al.*, 1949; Althausen *et al.*, 1950; Bothe *et al.*, 1954). The diet should contain an excess of calories (up to 3,000) to allow for the wastage, and be high in carbohydrate, and high or medium (Meyer, 1946) in protein. Starches are avoided as they increase intestinal fermentation and lead to cramps and distension (Althausen *et al.*, 1949). It is almost universal experience that these patients will thrive better if allowed a fairly wide choice of appetising foods and any attempt to "fortify" the diet with unpalatable protein hydrolysates, purées and the like simply results in a reduced intake and further loss of weight, and may aggravate the diarrhœa (Althausen *et al.*, 1949; Christensen *et al.*, 1950; Jackson and Linder, 1951; Berman *et al.*, 1953; Pilling and Cresson, 1957). Vitamins A, B, C, D and sometimes K (Christensen *et al.*, 1950) are required in amounts in excess of normal and may have to be injected when deficiency is established. If diarrhœa persists depletion of sodium and potassium may occur, but can usually be balanced by increased oral intake.

Attempts are made to slow down the rate of intestinal passage and opium has been found most effective, though autonomic ganglion-blocking agents are also useful (Brezin and Oren, 1954). The whole range of constipifacients should be tried in an effort to find the formula most suited to the individual. Vagotomy was without effect (Weckesser *et al.*, 1951; Marien and McCorriston, 1952).

Demulcents such as Tween-80 do not improve the fat absorption, though pancreatin has seemed of benefit to the patient without demonstrably reducing the fæcal fat loss (Christensen *et al.*, 1950; Pilling and Cresson, 1957). Roughage is usually avoided.

Calcium and iron in a soluble form are also prescribed and can be given by injection when the need is urgent and oral therapy is ineffective or too slow.

Cortisone has been used and seems on occasions to have improved the absorption of carbohydrate and fat (Adlersberg 1957). Diarrhœa has lessened and weight has been gained. Elsewhere cortisone and ACTH were without avail, or even harmful in other respects. Pregnancy has on occasions brought about a marked improvement in absorption (Montgomery and Pincus, 1955).

The effect of folic acid in reducing the fæcal fat is worth trial (Schwartz *et al.*, 1955). Capsules and tablets often appear unchanged in the stool and should be abandoned in favour of liquid or powdered preparations (Lawrence, 1953).

Comparison with Other Syndromes

The picture produced by massive resection is a combination of starvation and steatorrhœa, with the secondary effects of reduced calcium absorption and vitamin depletion. When compared with the findings in cases of sprue, idiopathic steatorrhœa, chronic small intestinal obstruction, blind loop and gastro-colic fistula certain differences appear. Anæmia of any kind is uncommon and hypoproteinæmia only terminal, while calcium absorption is often only mildly affected. The difference may be due to the presence of a length of normal gut, however short, as compared with the other syndromes in which the changes (probably bacterial) affect the entire length of small bowel.

REFERENCES

Adlersberg, D., ed. (1957) The Malabsorption Syndrome. Monograph of Mount Sinai Hospital. New York.

Althausen, T. L., Doig, R. K., Uyeyama, K., and Weiden, S. (1950) *Gastroenterology*, **16,** 126.

——, Uyeyama, K., and Simpson, R. G. (1949) *Gastroenterology*, **12,** 795.

Alvarez, W. C. (1948) An Introduction to Gastroenterology. 4th ed. New York.

Berman, J. K., Habegger, E. D., and Billings, E. (1953) *Amer. J. dig. Dis.*, **20,** 152.

Berman, L. G., Ulevitch, H., Haft, H. H., and Lemish, S. (1950) *Ann. Surg.*, **132,** 64.

Best, C. H., and Taylor, N. B. (1955) The Physiological Basis of Medical Practice. 6th ed. Baltimore.

Bothe, F. A., Magee, W. S., and Driscoll, R. H. (1954) *Ann. Surg.*, **140,** 755.

Brezin, D., and Oren, B. G. (1954) *Gastroenterology*, **26,** 895.

Brown, A. (1949) *Brit. med. J.*, i, 1073.

Bryant, J. (1924) *Amer. J. med. Sci.*, **167,** 499.

Christensen, N. A., Musgrove, J. E., and Wollaeger, E. E. (1950) *Proc. Mayo Clin.*, **25,** 16.

Clatworthy, H. W., Saleeby, R., and Lovingood, C. (1952) *Surgery*, **32,** 341.

Cogswell, H. D. (1948) *Ann. Surg.*, **127,** 377.

Cooke, W. T., Cox, E. V., Meynell, M. J., and Gaddie, R. (1957) *Lancet*, ii, 1231.

Eckstam, E. E., and Barry, G. R. (1954) *Wis. med. J.*, **53,** 548.

Erlanger, J., and Hewlett, A. W. (1901) *Amer. J. Physiol.*, **6,** 1.

Evans, H. M., and Brenizer, A. G. (1907) *Johns Hopk. Hosp. Bull.*, **18,** 477.

Flint, J. M. (1912) *Johns Hopk. Hosp. Bull.*, **23,** 127.

Gaynor, W. C. T., and Diefenbach, W. C. L. (1957) *N.Y. St. J. Med.*, **57,** 3681.

Harper, A. A., and Raper, H. S. (1943) *J. Physiol.*, **102,** 115.

Haymond, H. E. (1935) *Surg. Gynec. Obstet.*, **61,** 693.

Holman, C. C. (1944) *Lancet*, ii, 597.

JACKSON, W. P. U., and LINDER, G. C. (1951) *S. Afr. J. clin. Sci.*, **2,** 70, 205.
——, —— (1955) *Acta med. scand.*, **152,** Suppl. 306, p. 96.
KALLIO, K. E. (1932) *Acta chir. scand.*, **70,** 39.
KOSITCHEK, R. J., and RABWIN, M. H. (1950) *Amer. J. dig. Dis.*, **17,** 13.
KUNZ, H., and MOLITOR, H. (1928) *Arch. exp. Path. Pharmak.*, **132,** 50. (Abstracted in *ZentOrg. Chir.*, **44,** 463.)
LAWRENCE, C. H. (1953) *Postgrad. Med.*, **13,** 77.
MCCANCE, R. A., and WIDDOWSON, E. M. (1933) *J. Physiol.*, **94,** 148.
MCCLENAHAN, J. E., and FISHER, B. (1950) *Amer. J. Surg.*, **79,** 684.
MARIEN, B., and MCCORRISTON, J. R. (1952) *Amer. Coll. Surg. surg. Forum*, **3,** 123.
MARTIN, J. R., PATTEE, C. J., GARDNER, C., and MARIEN, B. (1953) *Canad. med. Ass. J.*, **69,** 429.
MEYER, H. W. (1946) *Arch. Surg.*, **53,** 298.
MILLER, D. K., and RHOADS, C. P. (1935) *J. clin. Invest.*, **14,** 153.
MONARI, U. (1896) *Bietr. klin. Chir.*, **16,** 479.
MONTGOMERY, T. L., and PINCUS, I. J. (1955) *Amer. J. Obstet. Gynec.*, **69,** 865.
OXENHORN, S., ESTREN, S., WASSERMAN, L. R., and ADLERSBERG, D. (1958) *Ann. intern. Med.*, **48,** 30.
PEARCE, A. E., ENTINE, J. H., and EKSTEROWICZ, F. C. (1953) *J. int. Coll. Surg.*, **20,** 322.
PETRI, A., NORGAARD, F., and THYSSEN, E. (1942) *Acta med. scand.*, **111,** 116.
PIETZ, D. G. (1956) *Gastroenterology*, **31,** 56.
PILLING, G. P., and CRESSON, S. L. (1957) *Pediatrics, Springfield*, **19,** 940.
POSEY, E. L., and BARGEN, J. A. (1948) *Surg. Clin. N. Amer.*, **28,** 903.
RHOADS, J. E., STENGELL, A., RIEGEL, C., CAJORI, F. A., and FRAZIER, W. D. (1939) *Amer. J. Physiol.*, **125,** 707.
SCHWARTZ, M. K., MEDWID, A., ROBERTS, K. E., SLEISENGER, M., and RANDALL, H. T. (1955) *Amer. Coll. Surg. surg. Forum*, **6,** 385.
SENN, N. (1888) *Ann. Surg.*, **7,** 99.
SHORT, A. R., and BYWATERS, H. W. (1913) *Brit. med. J.*, i, 1361.
TODD, W. R., DITTEBRANDT, M., MONTAGUE, J. R., and WEST, E. S. (1940) *Amer. J. dig. Dis.*, **7,** 295.
TRAFFORD, H. S. (1956) *Brit. J. Surg.*, **44,** 10.
TREVES, F. (1885) *Brit. med. J.*, i, 415.
WECKESSER, E. C., ANKENEY, J. L., PORTMANN, F. A., PRICE, J. W., and CEBUL, F. A. (1951) *Surgery*, **30,** 465.
WEST, E. S., MONTAGUE, J. R., and JUDY, F. R. (1938) *Amer. J. dig. Dis.*, **5,** 690.
WHIPPLE, G. A., and ROBBINS, F. S. R. (1936) *Amer. J. med. Sci.*, **191,** 11.
WILDEGANS, H. (1925) *Dtsch. med. Wschr.*, **51,** 1558. (Abstracted in *J. Amer. med. Ass.*, **85,** 1436.)
WILKIE, W. (1950) *S. Afr. med. J.*, **24,** 516.

DISCUSSION

Professor L. J. Witts: When President Eisenhower had a by-pass operation for regional ileitis, a number of people said to me, "Is it not dreadful about Eisenhower, having this blind loop created", but of course that is not the case. It is only quite a small proportion of patients with a blind loop who develop anæmia or other symptoms afterwards, and physicians prefer surgeons to go on treating regional ileitis by means of anastomotic operations rather than by resecting lengths of intestine. The development of anæmia and steatorrhœa seems to have something to do with a change in the intestinal flora and it may be greatly delayed. Sometimes a man may go for ten or fifteen years—I think we had one patient go nearly twenty years after an operation in which a stagnant loop had been created—before anæmia develops and in the majority it does not develop at all.

I was interested in the discussion of the site of resection. The earlier speakers emphasized that the jejunum has a much better absorptive surface than the ileum and one would think that when the jejunum was removed it would produce much more effect than when the ileum was removed. However, a good deal of experimental work suggests that removing the lower end of the bowel may be more harmful than removing the upper end and that this has to do with the slower rate of peristalsis in the ileum and the fact that the ileum acts as a second stomach. I would therefore support Mr. Pullan's view that whenever possible the lower ileum should be left.

Dr. R. H. Girdwood: I have been studying for some years now the question of bacteria in the small intestine, particularly in the "blind loop" syndrome. I agree that there are practically no bacteria normally in the small intestine, but from the small intestines of 7 patients, 5 with the "blind loop" syndrome and 2 with idiopathic steatorrhœa, there have been isolated 37 strains of organisms, mostly *E. coli*. These were obtained at operation, except in the idiopathic steatorrhœa patients, where the cultures were obtained at autopsy.

Studies are being made of what these organisms will do with vitamins and amino acids in culture media. One would expect them to take up vitamin B_{12} because the megaloblastic anæmia in the "blind loop" syndrome is due to vitamin B_{12} depletion and, in fact, all these organisms have taken up vitamin B_{12}. When radioactive vitamin B_{12} has been used in the culture medium, they have taken up the radioactivity. The work involved in this study is considerable, but so far it appears that the organisms can take up arginine, lysine, leucine and isoleucine, and that they do *not* take up folic acid, pantothenic acid, phenylalanine or methionine. They appear to be able to synthesize folic acid and possibly pantothenic acid, under very specialized cultural conditions. The work has been done aerobically so far, but anaerobic studies are under way.

SECTION III

Chairman—Professor C. G. Rob, M.C., F.R.C.S.

Medical Commentary on Disorders of the Small Intestine (Excluding the Duodenum)

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I propose to approach this medical commentary from the viewpoint of a practising physician rather than attempting an academic integration of the subject. As is obvious from the excellent papers we have heard, there has been substantial and exciting progress in our understanding physiologically and clinically of the small intestine. Nevertheless, one must admit at once that the small intestine remains an occult area, unlit by any endoscopy lights, difficult to intubate and sometimes poorly visualized radiographically. However, by patience and skill, one can do much to locate and identify organic disease of the small intestine. What we are less successful at doing is to unravel the subtle disorders of function which, no doubt, contribute to the so-called functional and nervous dyspepsias and the non-specific diarrhœas. Nevertheless, progress continues—already the secrets of the small intestine are being broadcast from little capsules containing minute transistor wireless sets and recording changes in pressure and pH. Within reasonable time, such diagnoses as enterospasm will either be substantiated by special motility tracings or refuted.

The small intestine intrudes into the clinical picture in considering such problems as steatorrhœa, chronic diarrhœa, abdominal pain, unexplained alimentary bleeding and anæmia, and I propose to consider each of these in turn.

Steatorrhœa

In this country steatorrhœa is the main clinical syndrome of malabsorption from the small intestine. I propose to discuss first the basic mechanisms leading to the development of steatorrhœa and then to review some of the clinical syndromes associated with it.

Malabsorption from the small intestine can be due to four mechanisms often closely interwoven:

(*a*) Inadequate mixing of food and intestinal secretions.

(*b*) Diminished supply of biliary and pancreatic secretions.

(*c*) Disorders affecting its secretory and absorptive efficiency.

(*d*) Abnormal bacterial activity in the small intestine with competition for essential nutrients.

Inadequate Mixing of Food and Alimentary Secretions

The loss of gastric digestive secretions which occurs, for example, in Addisonian anæmia, is of no consequence to the digestion of food and the small intestine deals very adequately with the breaking down and absorption of nutrients. This reminds us that the hopper function of the stomach is of primary importance. It acts as a reservoir permitting orderly emptying into the small intestine and the orderly and persisting stimulation of the pancreatic and biliary secretions. It is probably this loss of hopper mechanism which is the primary cause of the malabsorption in the intestine associated with partial gastrectomy and particularly with total gastrectomy. There is failure of co-ordination; put simply—bile and pancreatic secretions chase the food down the intestine instead of meeting and merging with it. It is likely that the loss of effective pancreatic function plays a major role in the steatorrhœa and resulting weight loss after the Polya type of partial gastrectomy.

Diminished Supply of Alimentary Secretions

This will naturally follow any extensive disease of the intestine, but may be a primary failure of a single constituent of a digestive juice or of an entire gland.

Steatorrhœa has been described due to a failure of bile salt production only and it is possible that some other cases are associated with a primary loss of a single component of the digestive juices. Alternatively, there may be the loss of a main contributor such as the pancreas. It is to be noted how very much better the body tolerates the loss of one component of digestion. Thus a patient with pancreatic deficiency may have tolerable health whereas an individual with adult cœliac disease with a lesser degree of steatorrhœa may be profoundly crippled.

Another particularly interesting mechanism has recently been noted in my department by my colleague, Dr. W. H. J. Summerskill, who found steatorrhœa associated with gross gastric hypersecretion of acid. This caused a very striking reduction of pH in the duodenum and upper part of the jejunum and the remarkable degree of acidity must have inactivated the pancreatic

enzymes in the upper few feet of the small intestine. Peptic ulceration, especially when atypical in site in the duodenum and upper jejunum and associated with steatorrhœa, can be explained on the basis of the Zollinger-Ellison syndrome with a non-insulin-secreting pancreatic adenoma which in some, at present unexplained, way causes a gross and persisting hypersecretion of acid.

Disorders Affecting Secretary and Absorptive Efficiency

Malabsorption must clearly follow if there is insufficient absorption area of small intestine. This can be due to surgical extirpation of intestine, short-circuiting of intestine either iatrogenically or by nature producing an internal fistula which can happen from inflammation of a diverticulum of the intestine or from perforation of a stomal peptic ulcer. Effective absorption from the intestine must be reduced if the mucosa of the intestine is damaged by a disease process, or if local disease of the small intestine causes a hold up. So-called idiopathic steatorrhœa has now been shown conclusively to be associated with diffuse atrophic changes. Widespread mucosal changes from other diseases such as Whipple's disease with mucopolysaccharide infiltration, amyloid disease, and lymphosarcoma can all lead to gross loss of small intestine function. Localized disease of the small intestine can cause delay in the passage of intestinal contents and this seems to impair absorptive efficiency, over and above the loss of the damaged portion of the intestine. This is the case with Crohn's disease, tuberculosis, simple stricture of the intestine or an annular carcinoma.

Abnormal Bacterial Activity

The final mechanism is the disturbance of intestinal function from the presence of an abnormal bacterial flora associated with the presence of a stagnant loop or pouch in the intestine—the "blind loop" syndrome. The same mechanism operates in causing the steatorrhœa associated with gastrocolic fistula. The "blind loop" syndrome mechanism contributes to the malabsorption after a Polya partial gastrectomy, in multiple diverticulosis of the intestine and in patients with Crohn's disease treated by short-circuiting procedures.

I propose to give a short clinical commentary on the various causes of steatorrhœa as they relate to the small intestine. Patients do not often come with a clearly established diagnosis, and sorting out the causes is one of the fascinations of clinical practice.

Dr. M. Shiner has discussed the semantic problems concerning the use of the term "idiopathic steatorrhœa". Cooke (1958) prefers the term "adult cœliac disease" but this may be only one subdivision and it may be preferable to retain the term "idiopathic steatorrhœa", recognizing that it may contain several subgroups which may be split off when they are clearly established.

Idiopathic steatorrhœa in its florid form is easy to recognize but even then one must exclude the secondary causes. The diagnosis has got to be considered not only when the stools are pale, bulky and offensive, and with continuing diarrhœa and weight loss, but also when there are intermittent bouts of loose stools or watery diarrhœa lasting for a few days and recurring several times a year and with relapses precipitated by some nervous or physical strain or by an unusually fatty meal. Constipation may exist between such attacks, intermittent nausea and vomiting may be a main feature and as gastric stasis may occur pyloric stenosis may be misdiagnosed. The diagnosis must be considered again often in the absence of any significant diarrhœa in patients with unexplained anæmia, unexplained cramps or tetany, or a bleeding tendency due in fact to deficient absorption of vitamin K. Again the clinical picture of Addison's disease with weakness and skin pigmentation may be closely mimicked by idiopathic steatorrhœa.

The diagnosis of "idiopathic steatorrhœa" rests on the demonstration of increased fat excretion by three-day stool estimations and finding more than 6 grams a day on a normal dietary intake. The diagnosis is confirmed by the demonstration of a histologically abnormal jejunal mucosa and a usually good response to gluten-free diet. The critical investigation is the finding of gross histological changes, and I have been fortunate in having the assistance of Dr. Shiner in studying my cases. With idiopathic steatorrhœa one expects to find:

(*a*) A reduced xylose excretion.

(*b*) Anæmia with macrocytosis, and associated with low serum B_{12} levels and impaired folic acid absorption.

(*c*) A flat blood sugar curve.

(*d*) An abnormal small intestine pattern radiologically.

The essential nature of idiopathic steatorrhœa is gradually becoming clearer and the present evidence has recently been summarized by Cooke (1958). It appears to be a familial constitutional disturbance and probably associated with a deficiency of an enzyme concerned with folic acid metabolism, but whether this is in the intestinal mucosa or liver is as yet uncertain.

Tropical sprue has to be regarded as basically different from "non-tropical sprue" or idiopathic steatorrhœa. There is a good clinical response to folic acid but no response to gluten-free diet. Intestinal biopsy does show some histological changes which are reversible and the folic acid test will return to normal.

Cooke (1958) has suggested that jejunitis which can on occasion simulate idiopathic steatorrhœa may prove to be the non-tropical counterpart of tropical sprue.

The causes of steatorrhœa secondary to a definite disease process are: pancreatic disease, internal intestinal fistula, Crohn's disease, intestinal tuberculosis, Whipple's disease, scleroderma, granulomatosis, jejuno-ileitis, blind loops, jejunal diverticulosis, inadvertent gastro-ileostomy, neuropathic diabetes, thyrotoxicosis, lymphosarcoma and other tumours involving the small intestine and following vascular insufficiency.

Pancreatic steatorrhœa, the only cause not directly involving the small intestine, may be diagnosed by duodenal intubation, blood sugar curve, and X-ray evidence of pancreatic calcification. There is no anæmia.

A history of previous abdominal operations may provide the clue to the presence of a blind loop. A dilated pouch associated with a side-to-side anastomosis can cause a blind loop with its attendant dangers. A barium meal should demonstrate a previous partial gastrectomy or gastroenterostomy but a barium enema will be needed to exclude a gastro-jejuno-colic fistula. Multiple diverticulosis of the jejunum may be easily confused radiologically with chronic intestinal obstruction, and multiple fluid levels should be carefully scrutinized with this possibility in mind. Radiology again will usually give a good lead towards the possibility of localized Crohn's disease or the rare diffuse jejuno-ileitis described by Cooke. In Great Britain active tuberculosis affecting the small intestine now seems to rank among the least common causes, but only thirty years ago it was accorded a major role for causing lacteal obstruction and steatorrhœa. Nevertheless, one is still entitled to look for tubercle bacilli in the stools, and I, personally, never treat a case of presumptive Crohn's disease with corticosteroids without anti-tuberculosis therapy as well.

Scleroderma, diabetes and thyrotoxicosis will be obvious from the case history. Whipple's disease is a fascinating rarity to diagnose. The association of arthritis, lymphadenopathy and pigmentation with diarrhœa raises the possibility, and the diagnosis can be confirmed by biopsy of a peripheral lymph node or by jejunal biopsy. The characteristic infiltration with mucopolysaccharides staining pink with the periodic acid Schiff technique establishes the diagnosis. In one case with which I was concerned the mesenteric lymph nodes were enormously enlarged, and deformed the duodenal loop, raising the possibility of carcinoma of the pancreas. I suspect that Whipple's disease is, in fact, a systemic disorder and the abnormal mucopolysaccharide is merely selectively deposited in the intestinal mucosa.

In older age groups particularly the possibility of lymphosarcoma or reticulosarcoma involving the mesenteric lymph nodes and mucosa is a very real one. A high white cell count is a possible clue but the diagnosis may not be made unless a laparotomy is performed.

Chronic Diarrhœa

Having discussed steatorrhœa I would like to consider the small intestine in relation to the rest of the clinical problem of chronic diarrhœa. It is here that much more basic work is needed in sorting out the mechanisms and causes of diarrhœa in relation to the small intestine. In the absence of more precise physiological knowledge one continues to classify diarrhœa anatomically and to think of small intestine diarrhœa as a group of patients with continued soft or often watery stools without blood or mucus and usually without periods of constipation. These may be due to the physical states affecting the small intestine which have already been referred to in considering steatorrhœa. A bigger problem numerically is those cases where thorough investigation is conclusively negative and yet a troublesome diarrhœa persists which one suspects is small intestinal and functional in character. These patients predominantly have nervous factors at least aggravating them. At one end of the scale there are the psychoneurotic individuals with lifelong bowel irritability started by some psychological problem long since lost in the unconscious although sometimes one gets an inkling of it. In lesser degrees they are individuals who had "expedition" diarrhœa as children with bowel looseness before any party or outing. Later in life any nervous tension hits their weak spot often precipitously. They are predominantly sensitive folk who get "bottled up" inwardly and they achieve an inner nervous tension which it is difficult for the more phlegmatic individuals to appreciate, but it is very real and an important factor to appreciate in the management of these individuals who can be enormously helped by a kindly understanding. Sometimes, however, one may fail to appreciate fully enough the personality of the individual and this was so with one of my patients worn out by personal difficulties and whom I sent to rest awhile in Devon—the poor town lady was petrified by the sight of cows

coming down the lanes and her bowels reacted very appropriately. However, my reputation was saved when I sent her to sit on the beach among the thousands at Clacton-on-Sea! One needs to know much more about the mechanisms in these cases and I hope that the recently developed technique of studying small intestine motility will provide a clue. One wonders if there is any physiopathological prerequisite. Could there be an excess of argentophil cells with overproduction of serotonin? Could there be an anatomical variation in the nerve plexuses? Could there be abnormal pathways within the brain so that emotional loads were short-circuited to the basal nuclei? There are other possible mechanisms for functional disorders of the small intestine. One has to keep in mind the possibility of habitual flogging of the bowels by aperients, sometimes a fact concealed by the patient and leading to even more serious episodes of illness from potassium deficiency and even necessitating urgent hospital admission. One of my female patients was under the impression, which personally I could not confirm, that without aperients there was some abdominal distension. To counteract this she took 2 to 4 vegetable laxatives daily which produced several pints of watery fæces a day, and indeed the husband was disturbed by the explosive sounds emerging from the lavatory and which could be heard all over the flat! She needed admission to hospital every three to six months for treatment of her potassium deficiency. The really difficult cases are those who conceal their taking of aperients but, fortunately, one can test for the common ones in the urine. Another possible mechanism of functional diarrhœa is the presence of abnormal bacterial activity in the small intestine which has already been discussed. With gross contamination and from blind loop or gastrocolic fistula a gross steatorrhœa results but it is possible that lesser degrees can exist and this may explain the bowel looseness in association with cirrhosis hepatis and probably other cases too. It is likely that there is abnormal breakdown of long chain fatty acids into the short chain and very irritating fatty acids. Allergy remains a possibility to consider. Occasionally one may determine a really clear-cut relationship but most often the cause is difficult and subtle such as a penicillin sensitivity from drinking milk from a cow receiving penicillin. The case for allergy in relation to diarrhœa has been often overstated but stripped of the enthusiasms of its exponents it remains as a small but significant facet of the problem. It need not necessarily be a true allergy as the experience of gluten sensitivity has shown. A simple elimination diet is a perfectly reasonable approach to some of the intractable cases of diarrhœa. There still remain patients without adequate explanation of diarrhœa—thyrotoxicosis has to be reconsidered. Another possibility, of which I have seen several examples, is a solitary small intestine diverticulum as a cause of continued or recurrent diarrhœa doubtless acting as a nidus of small intestine infection. Crohn's disease can be very difficult to diagnose in the early phase radiologically and must be kept very much in mind. Rarities such as carcinoid tumours of the intestine and the Zollinger-Ellison syndrome must be thought of. The problem of advisability of a laparotomy comes into the picture and my own bias is towards one if a nervous origin seems unlikely and it is the only certain way to make sure that the physical causes are eliminated.

Abdominal Pain

The small intestine will next be discussed in relation to recurrent pain. I personally doubt if it makes any appreciable contribution to the common functional dyspepsias, but there is a possibility of vascular ischæmia in older age groups leading to abdominal angina, and with discomfort coming on after meals, and also to steatorrhœa (Joske *et al.*, 1958). Acute indigestion with crampy pain coming on some time after a meal perhaps waking the individual at night may be due to a "bolus" colic with undigested pulpy food rolled into a ball and causing a physical obstruction. This is the mechanism of green apple colic in little boys! The same occurs particularly in adults after partial gastrectomy and eating whole oranges or incompletely soaked dried fruit, for these can lead to the complete clinical picture of intestinal obstruction—it is, in fact, a wise precaution to warn patients after partial gastrectomy of this possibility.

Enterospasm is a common explanation for recurrent and often severe pain particularly in women, and I have no doubt it is a mechanism, but one must consider carefully other factors which may produce severe spasmodic pain; porphyria, lead poisoning, hæmolytic crises, including nocturnal hæmoglobinuria, all turn up as occasional causes of recurrent and apparent small intestinal colic. Perhaps the same is true for drug addiction and in my own experience I suspect that a common perpetuating mechanism of a recurrent abdominal pain is pethidine or levorphanol, and an essential step in the management of such patients is to wean them from the opiates with the help of heavy sedation by barbiturates and Largactil. Recurrent small intestinal colic always raises the possibility of recurrent intussusception in relation to a polyp or carcinoma. A long history may tend to exclude this possibility, but in my experience carcinoma of the small intestine is an exceptionally slow growing

tumour and histories of three to eight years of recurrent pain sometimes coming on after meals is not uncommon. Anæmia plus the finding of occult blood in the stools makes a laparotomy imperative. Polyps may be adenomatous as with the Peutz-Jeghers syndrome or neurogenic, or a leiomyoma and one notes the presence or absence of pigmentation in the mouth and around the lips and looks for any stigmata of von Recklinghausen's disease.

Obscure abdominal pain may be part of the clinical picture of lupus erythematosus or periarteritis nodosa, the latter being due to discrete and multiple ulceration of the intestine. Less exotic but more important practically is intestinal infestation with tapeworm or round worm and this possibility must be excluded in all problems of obscure abdominal pain.

Alimentary Bleeding and Anæmia

The clinical problem of anæmia in relation to the small intestine depends on the interplay of impairment of absorption of iron, folic acid and vitamin B_{12}. Vitamin B_{12} is absorbed mainly from the lower end of the small intestine and low levels arise in several ways. There may be a primary deficiency of intrinsic factor. There may be competition for B_{12} by intestinal bacteria or by the *Dibothriocephalus latus*. There can be an intracellular defect of absorption in idiopathic steatorrhœa and regional enteritis correctable by steroids. Finally it may be due to resection of the lower part of the intestine.

Folic acid on the other hand is absorbed mainly in the jejunum (Cox *et al.*, 1958) and iron in the first 18 in. of the small intestine. Possibly in some patients this may be less and the length of the afferent loop after partial gastrectomy may be a vital factor in determining iron deficiency anæmia after the operation.

I would like to elaborate briefly the problem of blood loss anæmia in relation to the small intestine and I have learned to keep in mind certain unusual causes of intermittent blood loss. Von Willebrand's disease is a blood dyscrasia with a variable and abnormal bleeding time, and with family and personal history of increased bleeding tendency, and may be characterized by alimentary bleeding. True hæmophilia can also be a cause. Pseudoxanthoma elasticum (Grönblad-Strandberg syndrome) is a condition associated with widespread fragmentation of elastic tissue and a tendency to rupture of blood vessels within the alimentary tract causing recurrent hæmatemeses and melæna. The diagnosis is suggested clinically by finding a yellowish infiltration of the skin of the neck, axilla and groin associated with abnormal skin elasticity. One keeps in mind the possibility of other general medical conditions which can cause bleeding, Henoch-Schönlein purpura, chronic nephritis, amyloidosis and possibly occasional food allergy.

The local conditions of the small intestine causing bleeding include simple tumours, leiomyoma particularly, diverticulosis exceptionally but perhaps with enteroliths present, solitary ulcers of the intestine, ulceration associated with blind loops or idiopathic steatorrhœa. Another intestinal cause is telangiectasia as part of Osler's disease, also localized or diffuse hæmangiomatosis and aneurysms eroding the intestinal wall, arteriosclerotic, mycotic or syphilitic. All these occasional causes of intestinal bleeding can cause great difficulty in diagnosis.

Small intestine enemas, passage of Miller-Abbott tube may help in locating the lesion, as may the string test. Even at laparotomy a small lesion may be extremely hard to find and may be overlooked. For this reason, I believe the best time to do a laparotomy is when there is active bleeding. I have seen a leiomyoma previously missed twice at laparotomy discovered in this way.

In conclusion the diagnosis of small intestine lesions remains an exercise in patience and awareness of the many difficulties concerning this silent area of the body.

REFERENCES

Cooke, W. T. (1958) *Brit. med. J.*, ii, 261.
Cox, E. V., Meynell, M. J., Cooke, W. T., and Gaddie, R. (1958) *Gastroenterology*, **35**, 390.
Joske, R. A., Shamma'a, M. H., and Drummey, G. D. (1958) *Amer. J. Med.*, **25**, 449.

Surgical Commentary on Disorders of the Small Intestine

By John Bruce, C.B.E., T.D., P.R.C.S.Ed., (Hon.) F.A.C.S.

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The surgical commentator on disorders of the small intestine is confronted with a choice of approach—a difficult choice in a limited time and in a "mixed" company where matters of surgical technique are of only limited interest. He may choose to range widely—and perforce superficially—over a number of topics; or he may confine his survey to some particular facet of the problem. Each course has something to commend it; but I have elected to pursue the first, since it may serve to highlight the gaps in our knowledge of the small intestine and its diseases.

I can hardly escape some reference to current surgical technique, however, for it is now generally recognized that this is no longer the province of the surgeon alone. Very often the late sequelæ of our exercises in intestinal surgery

provide our medical colleagues with some of their most baffling and difficult problems in diagnosis and in treatment; and the task of interpreting symptoms and signs is rendered easier by some familiarity with the purpose and method of operation.

Until comparatively recently, surgical interest in the small bowel was concentrated on the acute emergencies to which it gave rise. For the most part these emergencies comprised the various forms of obstruction, and the occasional perforation of a simple ulcer or a malignant growth.

Acute Intestinal Obstruction

The high mortality attending the acute obstructions prompted a very avalanche of research which is now almost ancient history. As a result, the morbid physiology of ileus is reasonably well comprehended: it would be equally gratifying to claim that in consequence our therapeutic efforts had become universally and invariably effective. In fact this is not the case. Though there has been a steady decline in the overall mortality, in many places the death-rate from strangulation has not lessened, and some centres have actually recorded an increase.

The reason for this is all too obvious. It is a direct consequence of delay in identifying those types of obstruction that can be properly treated *only* by early operation.

Differentiation between the several forms of acute small bowel obstruction was formerly an academic exercise, since early surgical intervention was the rule in all varieties. Unfortunately, a simple surgical issue has been clouded by the success that sometimes attends the modern non-operative techniques of gastro-intestinal suction and intravenous fluid therapy.

Used in the correct circumstances—simple occlusion and paralytic ileus—these procedures may be effective and life-saving; they are quite ineffective—indeed, lethal—in strangulation, save as a part of the preparation for speedy operation.

It is unfortunate, perhaps, that even the patient with strangulation may be improved temporarily by suction and drip. This may appear to sanction delay in surgical intervention; but in the meanwhile the inexorable and inevitable progression to peritonitis and gangrene is not stayed, and ultimate recovery may be seriously jeopardized.

I suggest that it is high time we revised our current practice. The diagnosis of strangulation is sometimes easy—the "shock" of volvulus or infarction, the tender irreducible external hernia are unmistakable. But small internal herniæ—and, even more difficult, the strangulations round adhesions of a former laparotomy—may not differ significantly at the start from the simple occlusive obstructions. A constant area of abdominal tenderness instead of a generalized discomfort; rebound pain; and the persistence of pain between spasms of colic or despite suction are warnings that are too often ignored, with catastrophic consequences. No doubt the position would be improved by an increase in our diagnostic skill; but would it not be simpler to revert, after appropriate and purposeful pre-operative treatment, to our former policy of operation no matter what the type of the obstruction? Not only those with strangulation would benefit; for many simple occlusions also come to surgery, and often later than is desirable.

The modern "so-called" advances in the treatment of intestinal obstruction—suction, intravenous fluids and antibiotics—are in fact directed against the late effects of obstruction; early diagnosis and speedy operation could render their use unnecessary in a large majority of patients.

I have an idea that our registrars—on whom devolves much of the responsibility for this type of surgery—are confused and clinically unhappy. A more aggressive approach would both reduce the death-rate, and restore some measure of junior surgical equanimity!

A technical digression is perhaps admissible at this point. It seems that one of the deterrents to the acceptance of a policy of routine early operation is the difficulty of handling the distended coils of intestine, and the fear that splitting of the intestinal coats may occur when the support of the abdominal wall is withdrawn. In early cases the distension is largely gaseous, however, and this is obvious in "scout" films of the abdomen. Under these circumstances "deflation" by needle and suction, as recommended by Andrew Lowdon (1951), is a useful prelude to exploration, and an aid to other manœuvres. With care, even liquid contents can be evacuated safely.

Some Causes of Acute Obstruction

The pathological lesions that may produce obstruction are legion; but two to which reference has been made in this Symposium deserve a passing glance on account of the immediate and the remote problems they pose.

Mesenteric Vascular Occlusion

Massive infarction of the small bowel from arrest of either its arterial supply or its venous drainage is the most deadly of all acute strangulations. Few survive, and then only after resections of the most heroic order. The overwhelming mortality from operation, and the

fact that some recover on anticoagulant therapy alone has prompted many to avoid surgery at any cost. The truth is that only minor degrees of vascular occlusion without *complete* death of any portion of the bowel wall, or slowly developing occlusions, survive on an anti-coagulant regime. Complete focal infarctions, however small, demand operation on account of subsequent peritonitis.

The role of heparin therapy is therefore clear; for while it cannot relieve gangrene of the bowel wall, either limited or massive, it can prevent spread of the vascular thrombosis and is essential both before and after operation. It is worth recalling that though slow occlusion even of the superior mesenteric artery itself can occur without infarction, it is often followed by evidences of disturbed function. Furthermore, in such circumstances, later operative intervention may precipitate fatal infarction.

Obstruction by Small Intestinal Polypi

The second obstructing lesion that deserves scrutiny is the adenomatous polyp. This is the commonest simple tumour of the small intestine. Generally pedunculated, it may be a solitary lesion, or the mucosa may be studded with polypi of varying sizes. In the latter event, there may be associated brown pigmentation of the buccal mucosa, and/or the skin of the face and the fingers (the Peutz-Jeghers syndrome).

Acute obstruction is by secondary intussusception, and more often this is the event that brings the disorder to light; though hæmorrhage may be the first sign. Malignant transformation is very rare in contrast to the fate of the tumours of familial polyposis of the large intestine.

In polyposis the intussusception may be multiple, as in a patient of Professor Andrew Lowdon's who presented five separate invaginations at laparotomy; or it may be recurrent.

For this latter reason resection should be avoided whenever possible, and the offending polyp or polyps—and any others of substantial size—removed by enterotomy. Recurring resections lead to progressive reduction in the length of the intestine, and ultimately to a state of jejuno-ileal insufficiency.

Massive Resection of the Small Bowel and its Aftermath

The problems arising after extensive resection of the small intestine have been admirably reviewed by Mr. John Pullan and I have nothing significant to add to his survey. But one point is worthy of emphasis. It is important to recall that the full clinical picture of a malabsorptive state sometimes does not appear for a considerable time.

In one such patient an interval of more than three years elapsed before nutritional disturbance, anæmia and osteoporosis forced the patient to seek advice. For this reason, enthusiastic accounts of complete recovery following recent extensive excisions are interesting but essentially uninstructive.

It is my distinct impression that the site of the excision as well as its length affects the ultimate prognosis. So also may the underlying pathological state, and I have come particularly to dread even moderately extensive resections in the jejuno-ileal forms of Crohn's disease. I have sometimes wondered, indeed, if the florid lesions of this disease are not accompanied by a more widespread but not obvious change in the absorptive capacity of the intestinal mucosa.

Regional Enteritis (Crohn's Disease)

Regional enteritis, however, is a problem disease in every respect. A full consideration of its many features of interest is outwith the scope of this commentary, but I would like to remark on some points in its pathology, diagnosis and treatment.

Pathological Problems

The accepted criteria for the pathological diagnosis of this disease are those established by Crohn and his co-workers, and by Hadfield (1939). It is pertinent to inquire, however, if all intestinal lesions labelled as Crohn's enteritis are in fact the same disease.

Characteristic naked-eye lesions may display a quite atypical histopathology; they have occurred following the perforation of a solitary non-specific simple ulcer of the ileum, and after operation for a stenosing solitary ulcer of the ileocæcal region.

These peculiar ulcers were first described by Matthew Baillie in 1807; they are rare, usually ileal in location, and appear to have no relation to the peptic ulcer that may complicate a Meckel's diverticulum. The majority have been encountered at laparotomy for perforation, but there appear to be no follow-up studies of the eventual fate of such patients.

Usually the ulceration which occurs in Crohn's disease is only a small part of the subacute inflammatory process, but occasionally isolated ulcers are found elsewhere, away from the areas of frank enteritis; their significance is unknown. At the moment our knowledge of much of the pathology of the small intestine is far from complete.

Even the relationship of Crohn's disease to apparently well-established entities like tuberculosis and ulcerative colitis is not known. There seems no reason to doubt that *tuberculous*

ulceration of the small intestine can occur in association with active disease in the lungs or the larynx; and it has generally been assumed that apart from the rare congenital stenoses, and occlusions at the constriction ring of a former strangulated hernia or a previous anastomosis, *fibrous strictures of the intestine* are the result of healing with fibrosis of such tuberculous ulcers. In fact, similar strictures can occur in "burnt out" regional enteritis, or in areas where healing has occurred despite continued activity of the disease elsewhere.

The lesion commonly known as *hypertrophic ileocæcal tuberculosis* seems to have "disappeared" since the identification of Crohn's disease. Retrospective examination of so-called examples has generally disclosed a typical Crohn lesion; and some submitted to hemicolectomy have later presented with other intestinal granulomas with the characteristic Crohn pathology. There is obviously need for a review of the situation; and, in the meantime, it is wise to be cautious before applying a diagnosis of tuberculosis in chronic disorders of the small intestine.

Ulcerative colitis appears to be a distinct and different entity, certainly so far as pathology goes. But it has some undefined relationship to regional enteritis; for each may follow the other, and, though rarely, they may be found in association.

Diagnostic Difficulties

Two particular difficulties may be encountered —the differentiation between Crohn's disease of the terminal ileum and the functional ileal spasms, and the diagnosis of recurrence.

Pain and dysfunction as a result of spasm of the colon are a well-recognized entity, but it is only recently that a similar disorder of the small bowel has been recognized. It constitutes an important form of chronic obstruction, giving rise to episodes of colicky pain which may attain a considerable severity. Diagnosis is rendered difficult by the fact that often there are radiological signs of persistent stenosis and proximal dilatation of the small bowel, so that the radiologist is unable to exclude an organic lesion.

9 such patients have come under observation in recent years. The majority were young women, and in 2 the pain was so severe that laparotomy was undertaken on the suspicion of regional ileitis; the bowel was quite normal. In the others, the absence of a raised sedimentation rate and the absence of fever, signs of malabsorption or of anæmia justified a period of observation. In each case, clinical signs subsided, and the radiological deformity disappeared in three to six months.

I believe that a more acute and more vicious form of spasm is responsible for those occasional cases which present with all the clinical evidences of acute obstruction and yet a lesion is not discovered at operation. A series of such cases was recently reported by Dudley and his associates from my Unit under the title of "intestinal pseudo-obstruction" (1958).

The second diagnostic difficulty arises when symptoms recur after resection or short circuit. In most cases this is doubtless due to recrudescence or to spread of the disease; but there are two other possible explanations:

(1) Fibrous narrowing of the anastomotic stoma. Just as stenosis of an external ileostomy stoma can give rise to colicky pain and spurious diarrhœa—the syndrome known as "ileostomy dysfunction"—so may fibrosis of an internal stoma.

(2) A short-circuited "loop" may lead to steatorrhœa and all the systemic features of active regional enteritis.

The sorting out of these several possibilities may call for considerable patience and ingenuity. The corollary is that re-operation should be avoided until an accurate pathological interpretation of the symptoms is possible. Many would go farther and urge that operation should be avoided even in the primary treatment of Crohn's disease, save as a last resort. However, the innumerable problems in the management of regional enteritis would require a separate symposium, and I refrain from further comment at this juncture.

THE INTESTINAL "CUL-DE-SAC" SYNDROME

Fresh surgical interest in the small bowel was aroused by the demonstration by Witts and Watson (1952) that macrocytic anæmia and steatorrhœa sometimes follow operations which entail the formation of by-passed loops or cul-de-sacs in which intestinal contents can stagnate; and that disorders of this so-called "blind loop" syndrome may be relieved by appropriate surgical correction. Both Dr. Card and Dr. Avery Jones have discussed the mechanism of such functional derangements and the lesions that cause them, from the point of view of the physician and the investigator; the practical issues which are the surgeon's concern are of equal importance.

It is not yet sufficiently appreciated that anæmia may be a presenting symptom of small bowel disease in the absence of intestinal culs-de-sac. The microcytic anæmia of a lesion that ulcerates and bleeds is easily understood; but megaloblastic anæmia may dominate the clinical picture in such chronic obstructing lesions as constricting cancer or simple fibrous

stricture. The mechanism is probably the same as in the "blind loop" syndrome—stagnation above the obstruction, with a change in the nature, or the population, of the bacterial flora. Indeed, a clinical triad of abdominal cramps, megaloblastic anæmia and the presence of free hydrochloric acid in the stomach, in the absence of an intestinal "blind loop" or a previous gastrectomy should always rouse the suspicion of an organic obstructing lesion of the small gut, and prompt a careful follow-through radiological exploration.

Of the simple non-operative causes of "blind loop" symptoms, jejunal diverticulosis is one of the most fascinating. The condition is by no means rare; and until quite recently the diverticula were regarded as harmless pathological curiosities. They may bleed, even massively; they may become inflamed and perforate to form an abscess between the leaves of the mesentery; or they may give rise to megaloblastic anæmia and diarrhœa. So may diverticula of the duodenum, and I have recently had 2 such patients under my care. From the surgeon's point of view, the practical difficulty is the treatment of such cases. He is rarely fortunate enough to have only a solitary diverticulum to contend with; and there is no means of deciding which, or how many, of the diverticula are misbehaving, so that he may be confronted with the necessity for quite an extensive resection.

As surgeons, we are naturally most concerned with the disturbances of intestinal function and hæmatopoiesis that follow operation, and with the possibility of avoiding them. The extent of an intestinal resection is determined by the pathological lesion, but with other procedures it is now clear that: short-circuits should be avoided wherever possible; side-to-side anastomosis is inferior to end-to-end anastomosis; open anastomoses that permit mucosa-to-mucosa apposition are better than closed anastomoses over clamps. I imagine that these are matters on which surgical opinion would be undivided. There is less certainty about the relationship between stomach operations and subsequent nutritional disturbance.

Gastrectomy and Its Nutritional Sequelæ

The occasional occurrence of steatorrhœa and anæmia after partial gastrectomy of the Polya type has prompted the suggestion that a long loop—or stagnation in the afferent loop—might be responsible. Steatorrhœa may also follow the Billroth type of operation, however, and when it occurs after the Polya type of anastomosis it cannot always be relieved by converting the anastomosis to the Billroth variety. In my own experience, steatorrhœa and diarrhœa are rare complications of any kind of gastrectomy. In almost all of the patients I have seen with this complication there has been some additional factor: inadvertent gastro-ileal anastomosis instead of a gastro-jejunostomy, the presence of a "blind loop" from a previous intestinal anastomosis, such as duodeno-jejunostomy for so-called duodenal ileus, or a degree of pancreatic insufficiency, latent and not severe enough to be symptomatic until after the gastric resection.

Tumours of the Small Bowel

Small bowel tumours are rare and assume many guises. Thus they may cause acute or chronic obstruction, either by intussusception or by stenosis; they may perforate (as the lymphosarcoma and the carcinoid are prone to do); or they may cause anæmia from blood loss or from stagnation above a malignant stricture. The clinical postscript to this catalogue of disaster is that some tumours give rise to really massive hæmorrhage: hæmatemesis or bleeding *per anum*. The tumours most likely to behave in this way are the smooth muscle tumours, both simple and malignant. They do this by virtue of the tendency to central necrosis, which creates a kind of fistula between the intestinal lumen and the growth. This provides an interesting means of diagnosis, however; for the necrotic tract may be outlined by air or by barium.

In conclusion, then, it is obvious that disorders of the small intestine pose problems of great interest and great importance for the surgeon as well as his medical, radiological, physiological and pathological colleagues. In many instances, perhaps most, these problems are soluble only when the approach to them is not that of a single discipline, but a combined one with the resources of medicine and surgery fully mobilized both in diagnosis and in treatment.

REFERENCES

Baillie, M. (1807) The Morbid Anatomy of Some of the Most Important Parts of the Human Body. 3rd ed. London.

Dudley, H. A. F., Sinclair, I. S. R., McLaren, I. F., McNair, T. J., and Newsam, J. E. (1958) *J. R. Coll. Surg. Edinb.*, **3**, 206.

Hadfield, G. (1939) *Lancet*, ii, 773.

Lowdon, A. G. R. (1951) *Lancet*, i, 1103.

Witts, L. J., and Watson, G. M. (1952) *Brit. med. J.*, i, 13.

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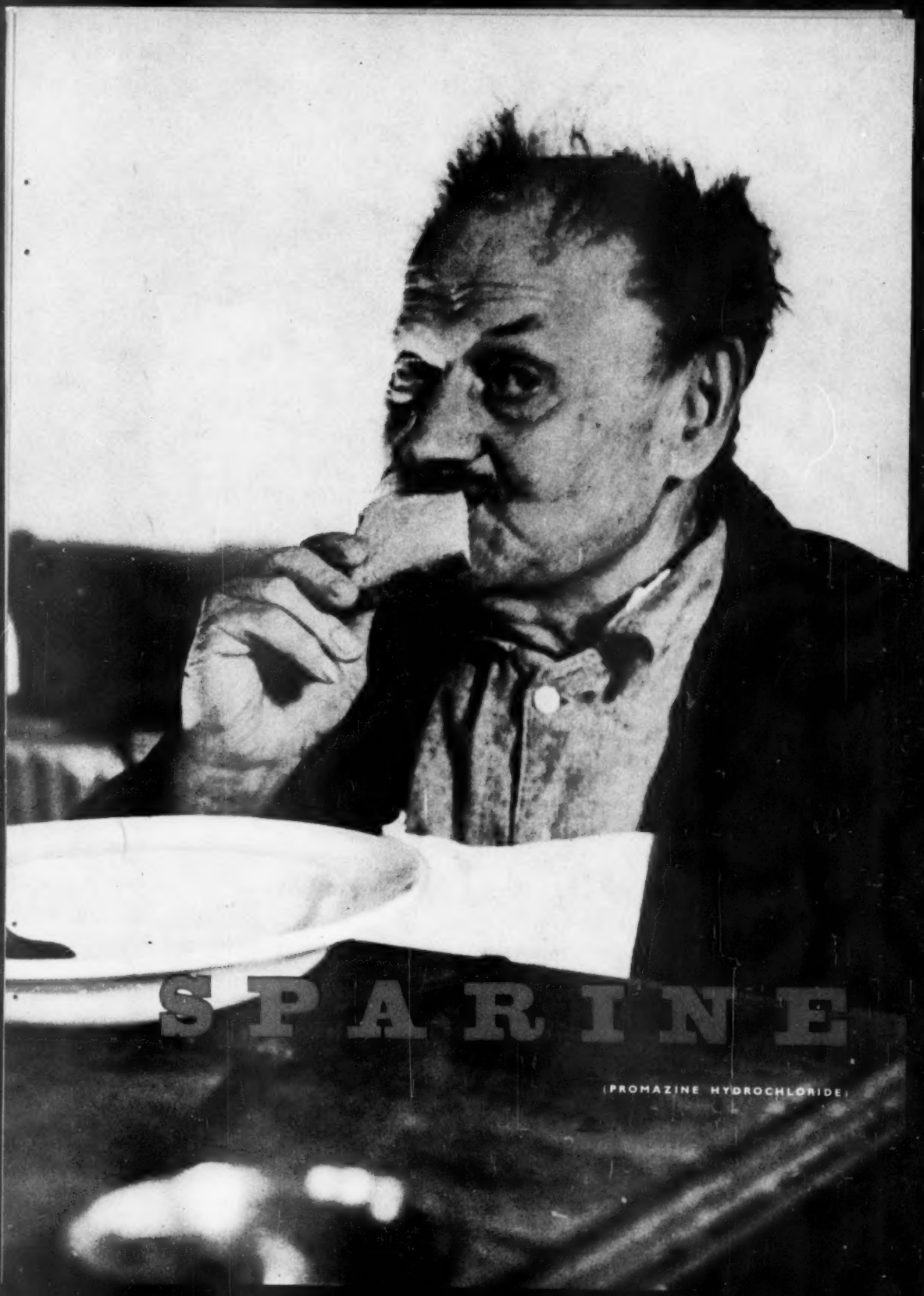
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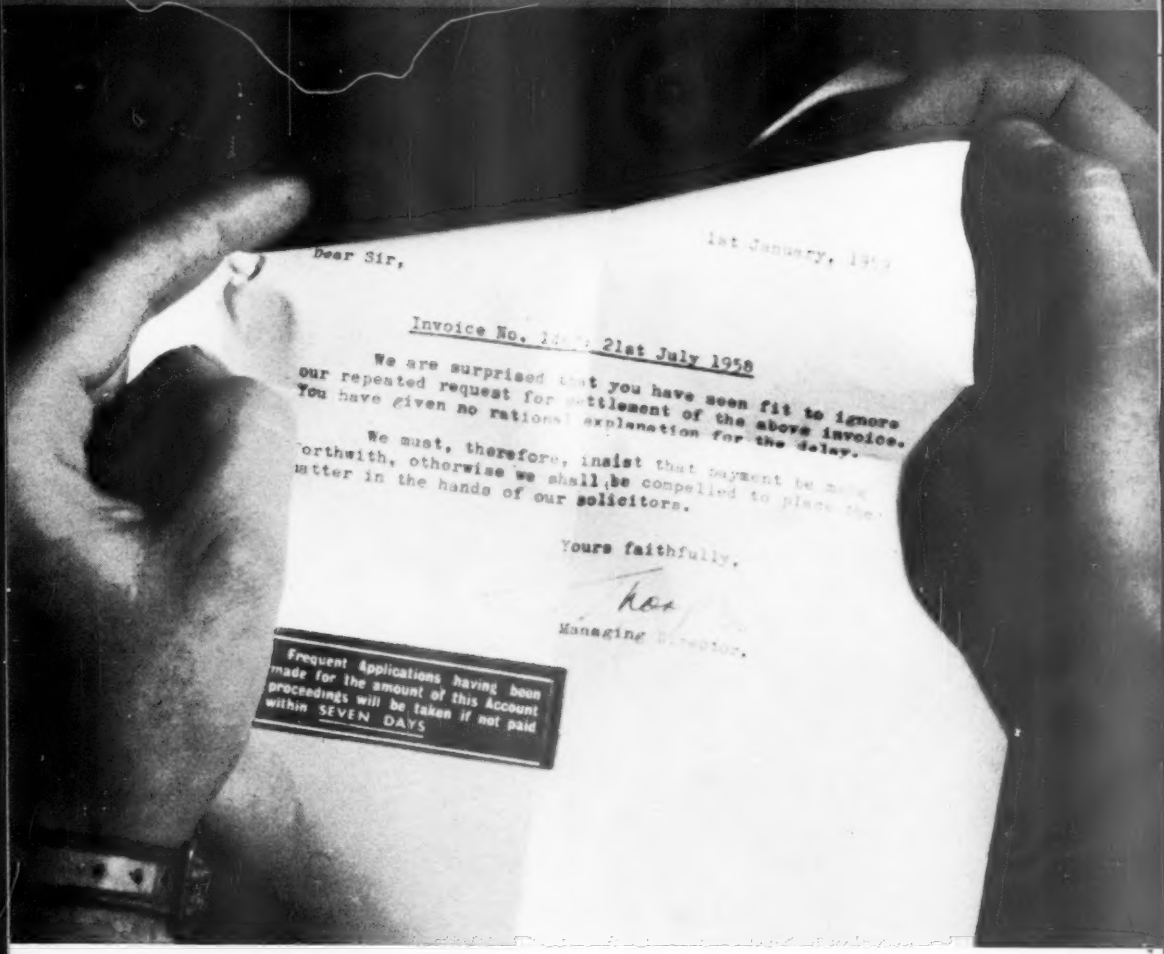
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1. Fouks, et al. (1956) Ann. med. psychol., **I**, 605.

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Chemopallidectomy and Chemothalamectomy for Parkinsonism and Dystonia[1]

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IN this paper I shall review our investigation into the effects of 850 globus pallidus and thalamic lesions in humans afflicted with parkinsonism and diverse involuntary movement disorders.

This series of cases commenced in 1952 with our investigation of the procedure of anterior choroidal artery occlusion for parkinsonism and was actually initiated by observation of the effects of a surgical accident. During the course of a craniotomy and pedunculotomy for uncontrollable tremor, I divided and was obliged to sacrifice the left anterior choroidal artery. Because of this occurrence, the operation was terminated in order to observe the effects of the occlusion of this vessel. The most notable post-operative finding was the virtual disappearance of tremor and rigidity of the opposite extremities without any loss of motor or sensory function of the arm or leg.

On the basis of this observation and earlier anatomical studies [1, 2] of the anterior choroidal artery a working hypothesis was developed to the effect that occlusion of the anterior choroidal artery had caused an infarction of several anatomical structures which had evolved as a physiological unit [3, 4]. It was further suggested that this unit consisted essentially of the mesial portion of the globus pallidus and the ventrolateral region of the thalamus as well as the connexions between these structures. Considerable evidence exists to support this hypothesis [5–15]. On that basis we proceeded to carry out an investigation of the effects of anterior choroidal artery occlusion in patients with parkinsonism (Fig. 1).

Between 1952 and 1955 selective anterior choroidal artery occlusion was performed in 55 patients. Follow-up examination of these 55 cases of anterior choroidal artery occlusion for a period ranging from two to six years following surgery demonstrates that in the successful cases this operation provided the most complete and lasting relief of far-advanced incapacitating rigidity, tremor and deformity that has been reported anywhere in the literature up until that time. Many of the patients who were completely relieved of tremor, rigidity and deformity from the side of the body contralateral to surgery have remained not only relieved of these symptoms for the intervening period up to the present time but have also become ambulatory and independent in their daily life.

Two cases with more than five-year follow-up studies are cited to demonstrate the complete and lasting nature of the effects of anterior choroidal artery occlusion in selected instances. These two cases are purposefully selected from among those originally described in my earliest reports.

Case I.—W. D., a 41-year-old white male, referred by Dr. Walter Friedman for occlusion of the anterior choroidal artery. This patient contracted epidemic encephalitis at the age of 15 and was in coma for six weeks. Parkinsonism developed within one year and by age 17 he was completely incapacitated by bilateral tremor and rigidity as well as the other manifestations of parkinsonism. At the time of operation he demonstrated masked facies, marked diminution of the spoken voice, a violent bilateral resting tremor, severe cog-wheel rigidity of all four extremities and inability to turn in bed, rise from a chair or stand or walk alone unaided. Of particular note at that time was the presence of a marked, apparently fixed deformity of the left wrist and hand of a dystonic nature. This had been present in this fixed form for eighteen years prior to operation.

On September 2, 1953, the right anterior choroidal artery was occluded by silver clips. This failed to obliterate the vessel completely. Therefore, re-operation was performed and the artery was coagulated so as to interrupt its blood supply completely.

From the time of surgery this patient has had complete relief of tremor and rigidity of the left extremities. However, even more remarkable was the reversal and disappearance of the dystonic deformity of the left

[1]From St. Barnabas Hospital and Division of Neuromuscular Diseases New York University Post-Graduate School of Medicine. Supported by Sister Elizabeth Kenny Foundation and Allen P. and Josephine B. Green Foundation.

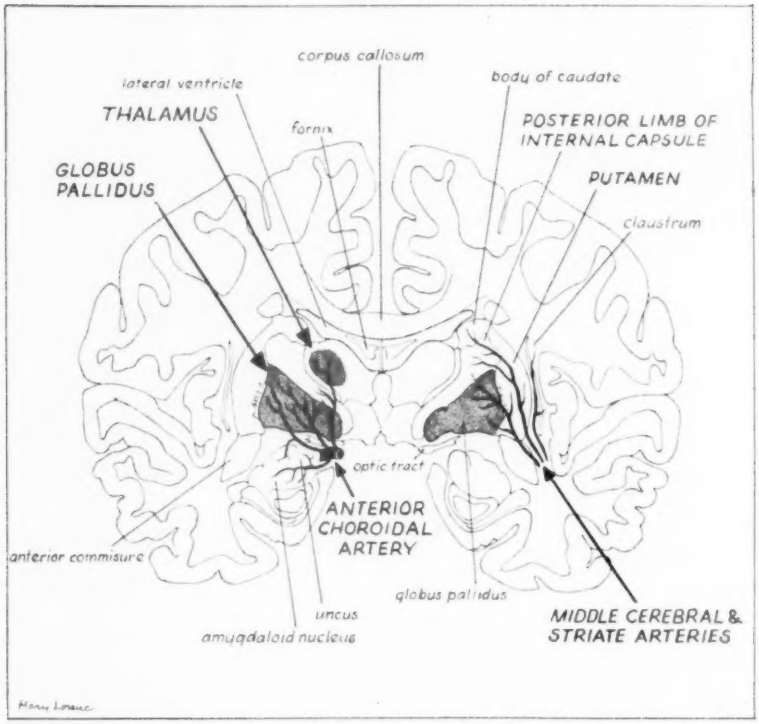


FIG. 1.—Diagrammatic representation of irrigation of basal ganglia of anterior choroidal artery.

hand. The patient became ambulatory and independent in all activities of daily living as a result of this operation. Relief of tremor, rigidity and deformity of the left extremities have persisted up to the present time.

Case II.—L. D., a 48-year-old white man, presented with marked tremor and rigidity present only in the left extremities of seven years' duration. Although still ambulatory and independent in his daily life, he was unable to work.

Anterior choroidal artery occlusion was performed in June 1953. Since that time the patient has had complete relief of tremor and rigidity of the left extremities with normal function of these extremities.

Complete relief of tremor and rigidity in this case is documented by a report of Dr. Christian Keedy who wrote in December 1956: "This patient has had a very excellent result from ligation of the right anterior choroidal artery. There is no evidence of any tremor or rigidity of the left extremities." An additional follow-up report from Dr. I. Perlmutter in October 1958 stated that the condition of the left side remains perfect. However, tremor and rigidity had slowly developed on the non-operated side.

These two cases demonstrate complete relief of intense tremor, rigidity, deformity and incapacity of parkinsonism achieved by occlusion of the anterior choroidal artery. It is stressed that the relief of contralateral tremor and rigidity obtained in these cases was complete, and that this fact is attested by disinterested examination of these patients by various objective neurological examiners. Moreover, the persistence of relief of tremor, rigidity and deformity in these cases for more than five years is noteworthy.

Conclusions which we reached as a result of the follow-up studies in these 55 cases of anterior choroidal artery occlusion are as follows: (1) The effectiveness of anterior choroidal artery occlusion, in those cases in which it was successful, was due to infarction of more than a single small anatomical structure and probably involved a physiological unit of 2 or more intercerebral structures: principally, the mesial part of the globus pallidus and the ventrolateral region of the thalamus. (2) Complete relief of tremor, rigidity, incapacity and deformity is possible by neurosurgical means without inflicting any neurological deficit upon the patient. (3) Objective evidence of five-year relief of the parkinsonian symptoms of tremor, rigidity and deformity has been achieved by anterior choroidal artery occlusion. (4) The dystonic deformities seen in some parkinsonians are not actually fixed

deformities but represent forced postures which are reversible even after many years' standing. (5) The so-called syndrome of the anterior choroidal artery is not invariable and in many cases this vessel may be occluded completely without producing any observable neurological deficit. However, anatomical variations of the vessel and particularly the lack of collateral blood supply to the posterior limb of the internal capsule in the aged would make routine employment of anterior choroidal artery occlusion unwise. (6) The ability of this procedure to relieve tremor and rigidity without inflicting any neurological deficit warranted further steps to develop neurosurgical techniques which might be more universally applicable to a broader spectrum of the parkinsonian population. This led us to the development of chemopallidectomy and thalamectomy which was commenced on our service in 1953 [11, 12, 13].

The techniques of chemopallidectomy and chemothalamectomy [14, 15] combine roentgeno-anatomical methods of lesion placement deep in the brain, with clinical physiological confirmation of the results in a conscious, co-operative patient. As presently performed the technique consists of the following basic steps: (1) Pneumo-encephalography with 30 c.c. of air in order to visualize the anterior portion of the ventricular system, especially the foramen of Monro. (2) Introduction of a polyethylene brain cannula through a small skull trephine. This cannula is placed under roentgenographic control into the region of the globus pallidus or ventrolateral nucleus of the thalamus. (3) Distension of a small balloon at the tip of the cannula in order to provide a clinical physiological test of the effects of a lesion in this region (*see* Fig. 2). In addition to providing such a physiological test the balloon produces a cavity in the desired region of the brain for subsequent injection of absolute alcohol and Pantopaque in order to produce a circumscribed and localized permanent lesion. (4) The cannula remains indwelling in the brain for several days following surgery so that the lesion may be enlarged if necessary in order to produce lasting relief of the contralateral hyperkinetic symptoms. The anatomical landmarks used in the production of these lesions are summarized in Figs. 3 and 4.

The production of a large lesion in the globus pallidus by the technique of chemopallidectomy proved to be a relatively simple procedure with a small morbidity and mortality rate and favourable results were obtained in 70% of cases. However, although rigidity could be relieved in 80% of such cases, tremor was relieved only in 60%. In such cases the tremor would respond favourably when we placed a second lesion on a plane approximately 10 mm. behind the original globus pallidus lesion or approximately 15 mm. behind the posterior margin of the foramen of Monro. Anatomical studies permitted us to identify the second area as a zone which included the pallidothalamic connexions with the anteroventral portion of the thalamus. In some instances the second lesion was localized within the ventrolateral region of the thalamus itself.

In subsequent experience with several hundred cases this latter lesion in the region of the ventrolateral nucleus of the thalamus proved to be so successful for cases that had been incompletely relieved of tremor by the pallidal lesion alone, that it gradually became our practice to produce a thalamic lesion primarily as the lesion of choice. We have learned that when this thalamic lesion is properly placed, virtually complete relief of

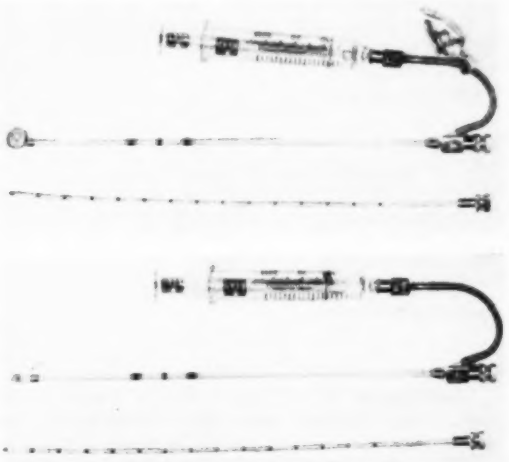


FIG. 2.—Special chemopallidectomy cannula, before and after inflation of balloon.

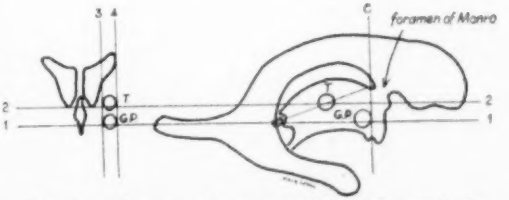


FIG. 3.—Diagrammatic representation of ventricular landmarks used for chemopallidectomy and chemothalamectomy.

tremor is obtained in 90% of cases of properly selected patients. Moreover, this relief is complete and is lasting.

There is no question but that a lesion in the region of the ventrolateral nucleus of the thalamus has a more certain, complete and absolute effect on contralateral resting tremor than does the pallidal lesion alone. It is now our lesion of choice for relief of tremor and rigidity.

From a surgical standpoint one must perform the technique meticulously, with accuracy in placement of the cannula and with persistence in production of an adequate sized, properly developed basal ganglia lesion.

From a clinical standpoint excellent relief of tremor and rigidity can be produced in more than 80% of properly selected cases. However, proper selection of cases is as important as correct surgical technique. The principal contra-indications to these operations at the present time are as follows:

(1) Organic mental deterioration.

(2) Psychosis.

(3) Pseudobulbar palsy.

(4) A preponderance of vegetative and akinetic symptoms as opposed to a preponderance of tremor or rigidity.

(5) Physiological old age. Although many cases have been operated upon successfully in the seventh and even in the eighth decade of life, one must select patients in this age group who are physiologically well preserved, do not show organic mental deterioration, and who have much more involvement of tremor and rigidity on one side of the body than on the other.

(6) General medical contra-indications such as severe hypertension.

Complications

The incidence of mortality in these 850 operations of chemopallidectomy and thalamectomy has been 2·4%. There has only been one post-operative death in the last 200 operations for parkinsonism on our service.

The incidence of lasting hemiplegia or hemiparesis has been 3%. Transient motor or sensory signs, disappearing during the first three post-operative weeks, have been observed in 6% of cases.

Some degree of somnolence, mental confusion or obtunding has been observed during the first post-operative week in 8% of cases; it may last several weeks in aged patients. However, this has invariably been transient, and in almost each instance has been an exaggeration of abnormalities noted during the pre-operative psychological work-up.

Speech disturbances, varying from dysphonia, to slurring of speech to mutism or aphasia have been observed in 7% of cases. They have been more common following operations on the dominant hemisphere but not limited to the dominant hemisphere operations. These disturbances have tended to clear within two weeks in practically every instance.

Excessive drowsiness, hyperpyrexia, hypokinesia, dysphagia, aspiration pneumonitis, and urinary retention are seen post-operatively in the far advanced post-encephalitic cases, but have responded to meticulous nursing measures.

Transient hyperkinetic states varying from slight fleeting choreic movements of one hand to hemiballismus have been seen 18 times. In three cases these were very severe but all disappeared spontaneously. One case, however, lasted four months.

Except for the isolated surgical complications such as deep hæmorrhage or infarction which account for our mortality rate of 2·4% and hemiplegia or hemiparesis of 3%, these transient post-operative problems seem to be directly related to the pre-operative condition of the patient, and can almost be predicted by the pre-operative evaluation. Although they are trying and often difficult to deal with in some instances, they do not affect the long range favourable effect of the operation on the patient or his symptoms.

In my experience the incidence of post-operative morbidity and complications is directly proportional to the condition of the patient pre-operatively. A patient who has unilateral parkinsonism, without other stigmata of far advanced disease, may be subjected to one of these procedures and have a reasonable expectation of having an excellent result and being discharged ambulatory from the hospital within ten days. A patient who is physiologically aged or who has far advanced bilateral disease, who has been bedridden or incapacitated for a prolonged period, and who has difficulties with salivation, speech, temperature control, swallowing, and other vital mechanisms, will often encounter transient difficulties which prolong hospitalization. It is in this latter group that one may expect to see transient confusion, hypopyrexia, bladder difficulties, and other post-operative abnormalities. These are of significance during the post-operative course but do not affect the long range favourable results of this type of basal ganglia surgery upon tremor and rigidity.

If these patients are on a post-operative ward which can supply meticulous, constant, interested nursing care and are under the control of medical attendants who have informed themselves of the protean nature of this syndrome and the various pitfalls which may be encountered post-operatively,

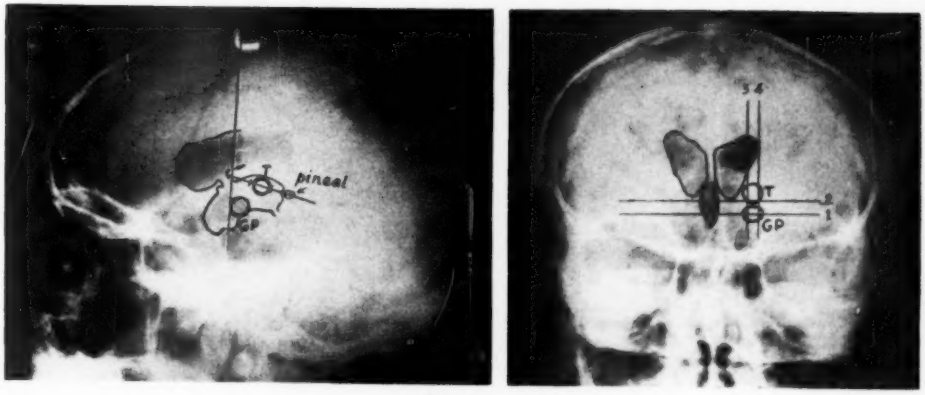


FIG. 4.

FIG. 5.

FIG. 4.—Landmarks of pallidal and thalamic lesions superimposed upon pneumoencephalogram.

FIG. 5.—Basal ganglia guide and holder employed in chemopallidectomy and thalamectomy.

FIG. 6.—Roentgenogram demonstrating balloon inflated within the region of mesial globus pallidus. Inflation of the balloon when correctly localized is followed by cessation of contralateral tremor and rigidity. This provides a physiological test essential to the technique of chemopallidectomy and thalamectomy.

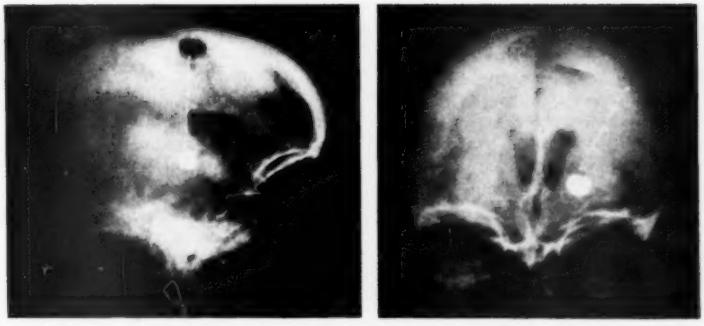


FIG. 6.

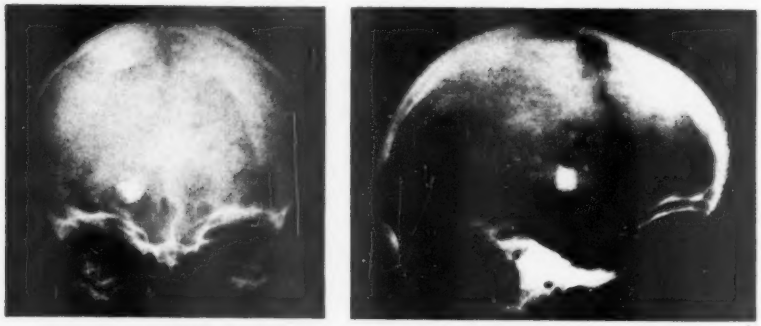


FIG. 7A.—Final alcohol-Pantopaque lesion produced by injection of this mixture into cavity formed by balloon distension demonstrated in Fig. 6.

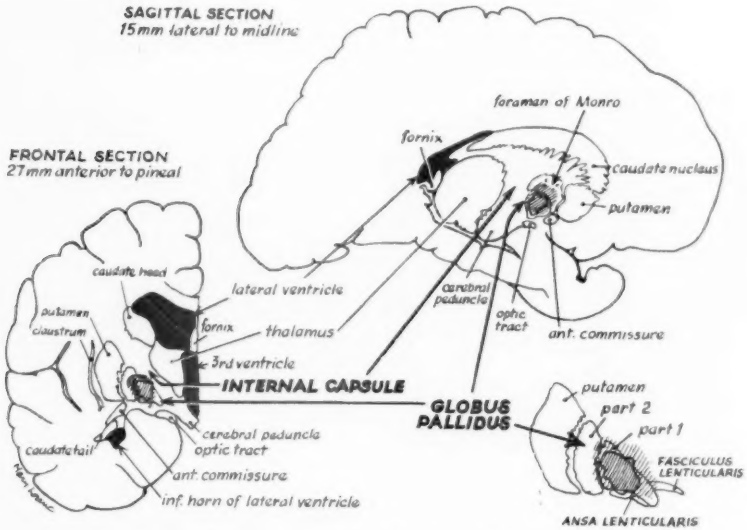


FIG. 7B.—Diagrammatic representation of anatomical site of lesion represented in Fig. 7A. Shaded area represents the lesion.

practically all of these trying post-operative complications can be either obviated or relieved. In surveying the statistics of this large series, in retrospect one is gratified at the fact that the trying and difficult post-operative manifestations referred to above have disappeared and that the overall rate of complications is minute compared to the lasting benefit which has been achieved in this group of chronically ill patients.

THE HYPER-PARKINSONISM CRISIS

From time to time during the post-operative period a patient will demonstrate a marked accentuation of all of the well-known features of the parkinsonian symptom complex. For example, we have seen on many occasions, during the first post-operative week, a patient, who has been successfully relieved of tremor and rigidity of the extremities contralateral to operation, manifest an exaggeration of all of the other symptoms of parkinsonism which he demonstrated prior to surgery. Such a patient may have increased difficulty in speaking, dysphagia, marked perspiration, hyperpyrexia, difficulty in voiding, increased tremor and rigidity of the non-operated extremities, hypersalivation with danger of

aspiration of saliva, and a marked increase in general helplessness.

This post-operative picture lasts about two weeks and clears gradually. However, during this crisis of hyper-parkinsonism, meticulous and constant nursing attention is necessary if one is to avoid aspiration pneumonia, decubital ulcers, urinary infection, and other complications that may ensue as secondary phenomena.

It seems at first glance paradoxical that one might encounter a transient marked exaggeration of so many parkinsonian symptoms in a patient who has actually been operated successfully for relief of tremor and rigidity of the extremities of one side of the body. However, one may see this same example of a crisis of hyper-parkinsonism in many non-operated parkinsonian patients who are subjected to a violent physical or emotional stress. For example, the elderly advanced bilateral parkinsonian who may fall and fracture his femur, often becomes totally helpless during the post-traumatic period as a result of exaggeration of all parkinsonian symptoms. Similarly, many patients with advanced parkinsonism do not become bedridden and helpless until subjected to the psychological stress of the death of a member of their family or some similar emotional duress.

This post-operative hyper-parkinsonism crisis seems to be related to the mental and physical stress of undergoing surgery plus the direct effect upon the brain. It is most commonly seen in post-encephalitic parkinsonians who present advanced symptomatology including symptoms of the vegetative variety as well as tremor and rigidity. One may see it as well in the aged parkinsonian. In the latter group, if this hyper-parkinsonism crisis is manifested post-operatively it is usually accompanied by transient mental confusion and disorientation.

We have commented in earlier publications on the importance of evaluating the effect of stress on each individual case of parkinsonism. It is our policy to insist on a period of hospital observation in any case of advanced parkinsonism in an aged patient in whom we suspect that stress might possibly precipitate exaggeration of the parkinsonian symptom complex. By so doing, we have found many cases of aged parkinsonians who, under the stress of strange hospital surroundings, manifest nocturnal hallucinations, confusion and disorientation. Such a patient, in our opinion, should no longer be considered as a candidate for surgery.

Similarly, we have found many patients, particularly in the far advanced post-encephalitic group, who, under the duress of frequent examinations and testing in a hospital environment become hyperpyretic, incontinent or retentive of urine, dysphagic, and generally helpless. Such a patient must be evaluated very stringently before making a final decision for or against surgery. If surgery is decided upon, one should anticipate the possibility of encountering this hyper-parkinsonism crisis as a transient complication during the first two post-operative weeks.

Many of the transient complications referred to above are actually seen to be features of this hyper-parkinsonism crisis which is a peculiar reaction of the parkinsonian to stress. In its extreme form it may change a previously compensated far-advanced bilateral parkinsonian into a hyperpyretic, dysphagic, speechless, motionless mass of protoplasm of a most frightening variety. Although such symptoms are reversible and will respond to good care, in many cases it is best to avoid these by a searching clinical inquiry prior to selecting any particular patient as a candidate for surgery.

These symptoms of hyper-parkinsonism are not precipitated following surgery on a case of unilateral parkinsonism or in those cases of parkinsonism who are not yet far advanced and do not show any evidence of mental deterioration. Therefore, as our experience has increased and we have been able to select patients more wisely than we did during the early years of this investigation, there are fewer patients on our wards manifesting this post-operative storm, and thus the incidence of transient complications on our post-operative wards has been commensurately decreased. At times it is just and wise to accept the calculated risk of producing this transient post-operative crisis because of the knowledge that it can be managed and that the patient will ultimately be benefited by the surgical treatment. However, by being aware that this hyper-parkinsonism crisis is practically a predictable sequence in certain types of cases the surgeon can either entirely avoid producing this post-operative storm or else knowledgeably risk its production because of the possible gains of surgery in a particular case.

Neurological Observations

A five-year study of all cases from a clinical psychological standpoint before and at various follow-up periods after operation has been carried out by our clinical psychologists. They have found that in no case has a lesion which has been circumscribed in the mesial globus pallidus or the ventrolateral region of the thalamus produced any lasting intellectual or emotional deficit.

In many instances large lesions have been placed on the same side of the brain in both the

globus pallidus and the ventrolateral portion of the thalamus. In such cases there has been no observable motor, sensory, or intellectual deficit. Thus, one may conclude that in selected cases relatively large portions of these structures in the basal ganglia may be sacrificed without interfering with voluntary motor movements or intelligence. The quantitative limits within which such procedures can be performed on both sides of the brain has not yet been established.

The placement of lesions in the thalamus is potentially more hazardous, because of the surrounding structures, than the placement of lesions within the pallidal complex. If one places the lesion inferior to the ventrolateral nucleus of the thalamus, the corpus luysii and its environs are penetrated and the possibility of production of hemiballismus is present. Immediately lateral to the properly placed thalamic lesion is the internal capsule, involvement of which will produce hemiparesis. Theoretically, placement of a lesion posterior to the ventrolateral nucleus of the thalamus should result in sensory loss because of involvement of the sensory area of the thalamus. However, in only two instances have we observed any gross sensory defect post-operatively in this group of patients. Moreover, in not a single instance have we observed the so-called thalamic pain syndrome following placement of thalamic lesions.

It is our impression that interruption of cerebello-thalamic as well as other afferent systems to the thalamus, including pallido-thalamic and rubro-thalamic connexions, contributes to the relief of tremor and rigidity following placement of a lesion in this region.

Documentation

In 1955 Doctors Robert S. Schwab and Albert England of the Massachusetts General Hospital in Boston instituted an objective evaluation of our cases of anterior choroidal artery and chemopallidectomy. Later, a mutual study was initiated in which long-term cases from their clinic in Boston were operated upon by us and were re-evaluated post-operatively by Schwab and England. Their study of our cases corroborated the fact that lasting complete relief of tremor, rigidity and deformity is achieved by these techniques without necessarily inflicting any neurological or emotional deficit. Further, during the week of May 12, 1958, we brought back to New York University 100 follow-up patients who had gone from one to more than five years following operation for parkinsonism on our service. These patients were made available with their complete objective investigative records and cinematographic records for disinterested follow-up evaluation.

One other clinical reference may be indicated at this time. In view of the possibilities of surgical therapy in certain varieties of parkinsonism, a re-classification of this syndrome might be considered. The therapeutic possibilities which currently exist in many cases of the shaking palsy require intensive clinical study and selection by the clinician if the proper therapy is to be utilized. A re-study and re-classification of the various types of parkinsonism and the subdivisions of this syndrome would be useful both therapeutically and in an enhancement of our ultimate physiological understanding of the disease process. The following are some representative cases:

Case III.—Dr. N. A., a 63-year-old chemistry professor, was referred by Dr. Albert England of Boston. This patient had a four-year history of tremor of the left side of the mouth, left upper extremity and left lower extremity. He dragged the left leg when walking. He demonstrated a violent tremor with marked rigidity of the left extremities but only a trace of tremor in the right upper extremity. On June 14, 1957, chemothalamectomy was performed. The roentgenographic appearance of the Pantopaque-stained, chemically induced thalamic lesion is seen in Fig. 8A. An approximate anatomical interpretation of this lesion based upon our own anatomical researches as well as reference to the atlases of others is provided in Fig. 8B. This demonstrates what we consider to be the lesion of choice for treatment of tremor and rigidity of parkinsonism. In this regard it is interesting to note the follow-up report of Dr. England, the referring neurologist, who also examined the patient at various intervals post-operatively. Dr. England reported: "This is a grade A perfect result. I think this complete functional result without any trace of either tremor, rigidity or loss of co-ordinated movements is very important. It has apparently gone beyond controlling tremor or rigidity and approached the so-called perfect result."

This case is cited as an example of complete relief of tremor and rigidity by a chemically induced thalamic lesion.

Case IV.—Reverend N. T., age 51, noted onset of tremor in the right upper extremity four years prior to admission to our service. Tremor and rigidity of the right extremities had progressed rapidly during these four years and became violent under emotional duress. These symptoms made it impossible for him to continue his calling as a minister.

On October 31, 1957, chemopallidectomy was performed. At this time a lesion was made at the level of the posterior border of the foramen of Monro. However, slight tremor of the right upper extremity persisted, particularly during emotional duress.

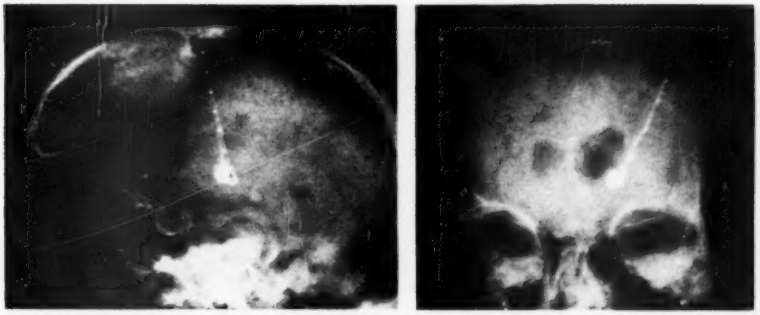


FIG. 8A.—Roentgenographic appearance of thalamic lesion produced in Case II. In our experience this is the lesion of choice for complete alleviation of tremor and rigidity.

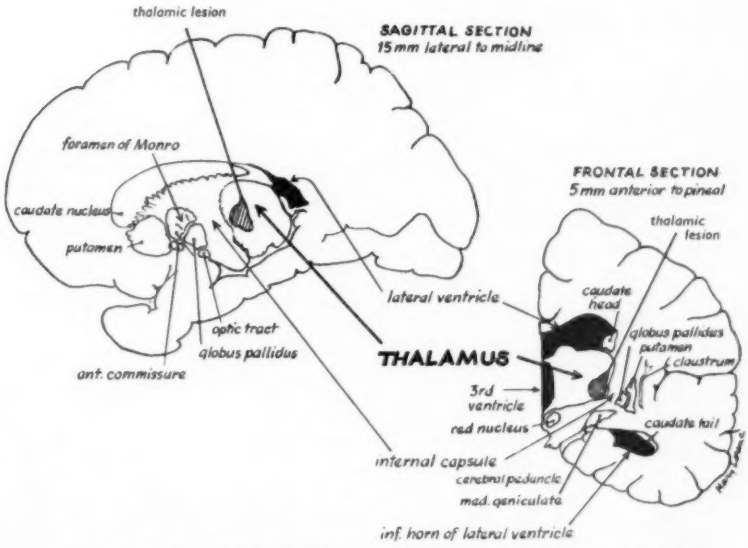


FIG. 8B.—Anatomical interpretation of roentgenogram in Fig. 8A. Shaded area represents the lesion.

Therefore, on November 15, 1957, a second lesion was placed in the region of the ventrolateral nucleus of the left thalamus. From that time to this there has been no further tremor or rigidity of the right extremities. The patient is now once again engaged in his profession as a minister and is in charge of the parish which he had previously been obliged to relinquish. He has not taken any anti-parkinson medication since operation. The patient, his family, and the referring neurologist all state that he appears completely normal.

The lesions of the globus pallidus and thalamus are shown in Fig. 9A. Our approximate anatomical interpretation of this roentgenogram is demonstrated in Fig. 9B.

This case is cited to demonstrate a perfect result regarding relief of tremor and rigidity induced by a combined pallidal and thalamic lesion. This combined lesion did not result in any motor, sensory, intellectual or psychological deficit. As a result of these lesions this patient who was disabled by violent unilateral tremor and rigidity now appears as a normal individual. The operation was performed in the dominant hemisphere without any adverse effect upon speech. This patient now regularly addresses his congregation each Sunday without difficulty.

One should note in this case the value of persistence in production of basal ganglia lesions.

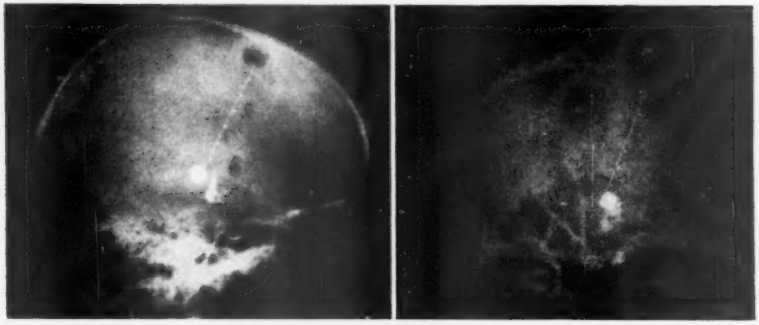


FIG. 9A.—Roentgenographic demonstration of alcohol-Pantopaque pallidectomy lesion followed by insertion of balloon cannula into the thalamus in Case IV.

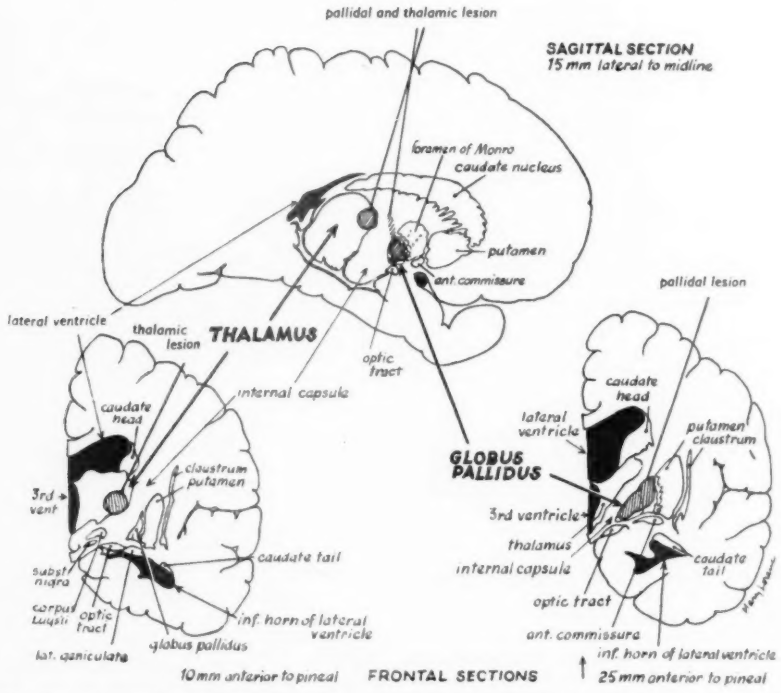


FIG. 9B.—Anatomical interpretation of roentgenogram demonstrated in Fig. 9A. The pallidal lesion and thalamic balloon placement are indicated by shaded areas.

We have constantly stressed that if a globus pallidus lesion renders an incomplete result, it should be followed by a thalamic lesion as illustrated by this case. This type of case would now receive a thalamic lesion as the primary one on our service.

Case V.—Miss A. B., a 60-year-old nurse, was referred by Dr. James Cooney of Florida. She had

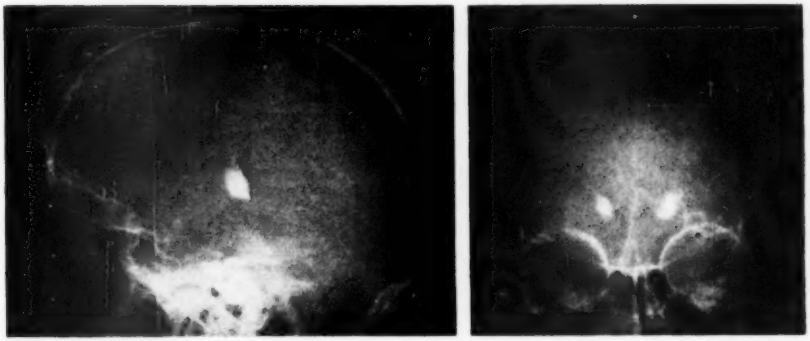


FIG. 10A.—Roentgenographic appearance of bilateral thalamic lesions produced by alcohol-Pantopaque injections in Case V.

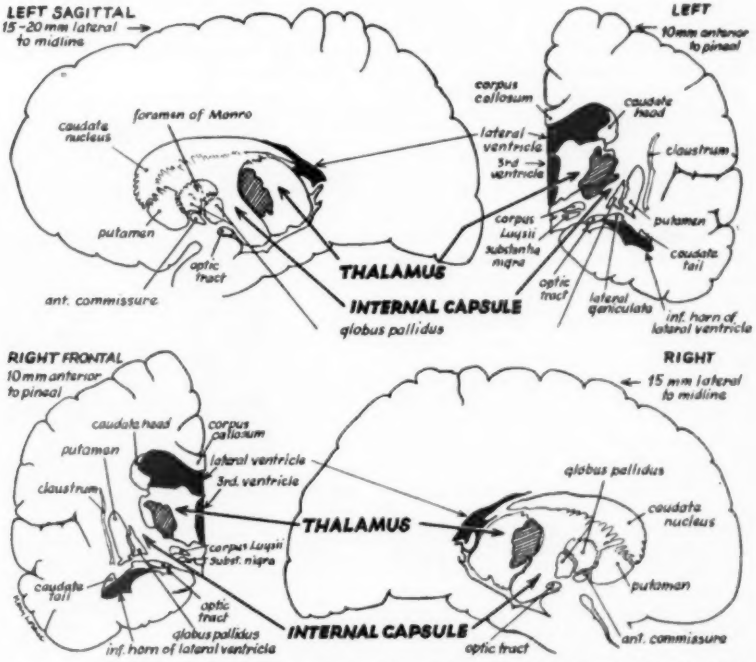


FIG. 10B.—Shaded areas represent anatomical interpretation of bilateral thalamic lesions demonstrated in Fig. 10A.

a six-year history of tremor and rigidity of the left extremities. Progression of her symptoms made walking difficult and finally made it impossible for her to continue her work as a nurse. During the year prior to admission there had been onset of symptoms in the right extremities. Right chemothalamectomy was performed October 24, 1957. This resulted in complete relief of tremor and rigidity of the left extremities which has persisted to date. In May 1958 a left chemothalamectomy was performed for relief of tremor and rigidity of the right extremities. This operation was also successful. Therefore, the patient

has had complete relief of tremor and rigidity of all four extremities as a result of bilateral chemothalamectomy (*see* Fig. 10A, B).

This case demonstrates bilateral thalamic lesions inflicted in a 60-year-old female with complete lasting relief of tremor and rigidity on both sides of the body, and shows the possibility of carrying out chemothalamectomy on each side of the brain. However, experience with the bilateral operation is still limited and requires further experience and investigation before the quantitative limitations of this type of surgery can be explicitly stated.

Case VI.—K. K., a 14-year-old boy from Chicago, Illinois, was referred because of a confirmed diagnosis of dystonia musculorum deformans of three years' duration. The illness began with an abnormal involuntary turning motion of the left ankle. By the time of admission the patient had a marked opisthotonic deformity of the neck and trunk. The left extremities had typical torsion movements and deformities. There was flexion and adduction of the left hip with exacerbation of the lumbar lordosis. The right extremities were involved to a lesser extent as regards deformity but had rather marked involuntary movement disorders. It was impossible for this patient to sit unsupported or to lie comfortably in bed. He often had to sleep on the floor. He could not walk without support. It was impossible for him to attend school.

On September 7, 1957, the patient had a right chemopallidectomy. This was followed on October 1, 1957, by right chemothalamectomy. This produced marked alleviation of the symptoms and deformities of the left extremities. The marked torticollis and opisthotonus of the back continued. Symptoms progressed in the right extremities. In February 1958 a left chemothalamectomy was performed. Following this procedure the patient had marked improvement in movements of the right extremities and also had alleviation of the dystonic deformities of the neck and trunk.

From that time to this there has been marked progressive improvement in this boy's condition as illustrated in Fig. 11.

The patient appears virtually normal at this time. He now rides a bicycle, plays golf, has returned to school and engages in all academic and extracurricular activities which are normal for a boy of his age. His parents report that he is completely independent in all of his activities and is able to travel about town alone without difficulty.

His parents have written on many occasions stating that they now consider him to be returned to normal. Dr. Joshua Spiegel of Chicago has recently examined this boy as an objective observer and reports: "This is a splendid result. During the 45 minutes that this boy was in my office I did not find any evidence of deformities or involuntary movements of any kind."

This case is cited as an example of the reversibility of dystonic deformities and movements by chemopallidectomy and thalamectomy.

FIG. 11A.—K. K. (Case VI) prior to bilateral operation showing deformities of dystonia musculorum deformans.

FIG. 11B.—K. K., following operation, illustrating post-operative relief of deformities and movements of dystonia musculorum deformans.

DISCUSSION

A perusal of the representative cases cited above and an examination of the roentgenographic appearance of the basal ganglia lesions produced as well as the anatomical interpretation of these lesions demonstrate that it has been possible to relieve tremor, rigidity, deformity, bradykinesia

and incapacity by lesions placed within a complex consisting of the ventrolateral nucleus of the thalamus, the ansa and fasciculus lenticularis, and the mesial globus pallidus. Such lesions are capable of completely alleviating a contralateral tremor and rigidity without infliction of any observable motor, sensory, intellectual or psychological deficit.

Until it becomes possible to examine many of the brains in which such successful lesions have been inflicted, the exact nuclei and pathways which are principally involved by these successful lesions cannot be stated with certainty. However, it is our impression at this time that the lesion of choice for relief of tremor and rigidity is one placed in the region of the ventrolateral nucleus of the thalamus. Further, we believe that it is the interruption of the pallido-thalamic, cerebello-thalamic, and rubro-thalamic impulses which are principally responsible for the complete relief of tremor and rigidity produced consistently by this lesion. That is not to say that other pathways and impulses may not be involved. However, the confluence of these particular pathways upon the ventrolateral nucleus of the thalamus and their interruption by the lesion of chemothalamectomy lends itself to this interpretation.

The size of the lesion which one should inflict in order to obtain relief of symptoms must be decided in each individual case. Obviously, the lesion must be large enough to relieve the symptoms completely, but should not encroach on any structures which will produce undesirable sequelæ. In our opinion the ability to graduate this lesion in small increments in a conscious, co-operative patient, as is done in chemopallidectomy and thalamectomy, is logical, effective and rewarding. Many academic objections can be posed to chemical lesions as well as to other types of destructive brain surgery, but the ultimate proof remains the relief of disabling symptoms in a human being without inflicting any undesirable side-effects. The method of lesion production employed in our service in more than 850 operations fulfils these criteria and provides complete relief of tremor and rigidity in a singularly successful manner.

In this respect I must insist that it has been our goal during this six-year investigation to study the problem of parkinsonism and its surgical treatment. Consequently we have attached ourselves to the problem including the important, basic investigation of the syndrome and its manifestations. Those who attempt to master a single surgical technique rather than to understand every possible ramification of the disease process will not achieve consistently beneficial results from surgery. Because of our basic interest in the problem rather than in a single surgical technique, there has been at least one major change in our surgical technique during each of the six years of this investigation. Modifications have ranged from occlusion of the anterior choroidal artery, to the free-hand method of globus pallidus injection, to the technique of use of an indwelling cannula, to development of the chemopallidectomy cannula guide, to use of a balloon to provide a physiological test and create a basal ganglia cavity, and finally a modification of the surgical target from the globus pallidus to the thalamus as the lesion of choice.

It is my hope, and I believe that our cases and the end-results in our patients bear out this aim, that the gradual modification of chemopallidectomy and thalamectomy reflects our insistence upon the necessity of modifying any technique with increasing knowledge and insight into the problem, to which the technique is only an accessory. In this regard, I feel strongly that the performance of this type of surgery under modified local anæsthesia, so that the surgeon may obtain clinico-physiological verification of the result of cannula placement and balloon insufflation, is a *sine qua non* of consistently good results with complete relief of contralateral tremor and rigidity.

Anatomical verification by X-ray, no matter how accurate, cannot by itself supplant the usefulness of this physiological test at the time of surgery and during gradual infliction of the lesion. I believe that it is this physiological test, originally performed by procaine injection and more recently by balloon insufflation in the globus pallidus or thalamus, that is the singular feature of chemopallidectomy and thalamectomy which distinguishes it from techniques solely dependent upon anatomical localization. Important as accurate anatomical identification may be, the ultimate result of relief of tremor and rigidity is even more important both to the patient and to the surgeon. Physiological verification by the cannula balloon technique helps immeasurably to assure this desired result.

Conclusions

A five-year follow-up study of more than 850 operations of anterior choroidal artery occlusion, chemopallidectomy and chemothalamectomy leads to the following conclusions:

(1) This investigation has resulted in a practical roentgeno-anatomical-physiological method of basal ganglia surgery which can relieve tremor and rigidity of parkinsonism in more than 80% of properly selected cases with a risk of mortality of 2·4% and a risk of hemiparesis of 3%.

(2) Tremor, rigidity, deformity and incapacity of

parkinsonism can be relieved without the infliction of any neurological or psychological deficit.

(3) Five-year cures of the symptoms of tremor, rigidity, deformity and incapacity can now be documented in this series of cases.

(4) Parkinsonism can no longer be considered as a hopeless, progressive, incurable disease. Inasmuch as the incapacitating symptoms of tremor, rigidity, and deformity have been alleviated for as long as five years without recurrence by surgery of the globus pallidus and thalamus, a more hopeful and optimistic viewpoint can be adopted concerning this disease. The therapeutic implications of this statement apply not only to surgical therapies but to the future development of medical treatment as well. Moreover, the symptoms of dystonia musculorum deformans have been alleviated during the course of this study for periods up to three years without recurrence.

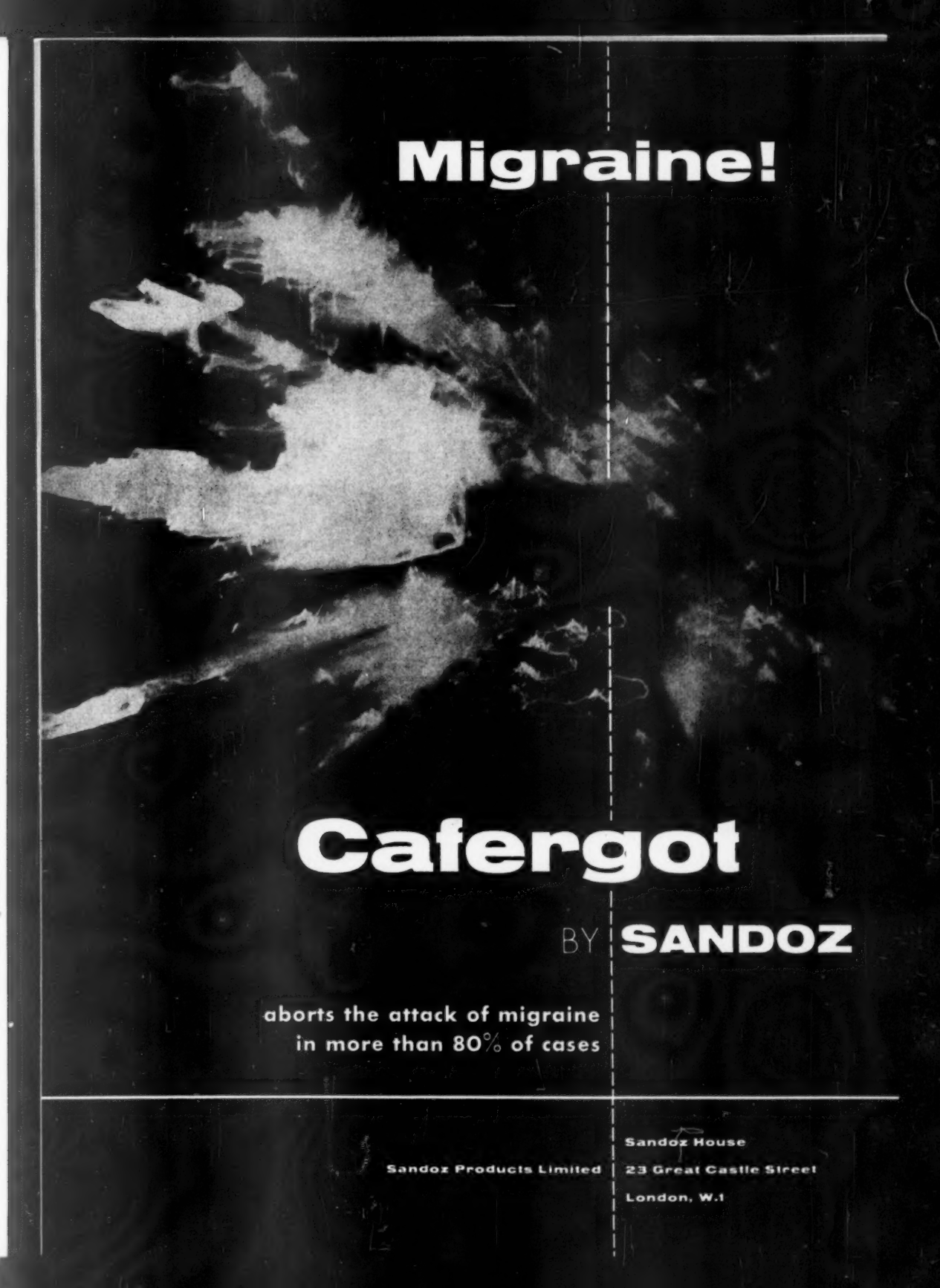
(5) The treatment of choice of many cases of parkinsonism and of dystonia musculorum deformans is surgery of the globus pallidus and thalamus. The thalamus is the surgical target of choice.

(6) Lesions confined to the globus pallidus and/or ventrolateral region of the thalamus on one side of the brain do not result in any motor, sensory, intellectual or psychological deficit. The degree to which such lesions can be inflicted on both sides of the brain requires further elucidation.

(7) Clinical studies leading to a more physiological classification of the subdivisions of the overall parkinsonism syndrome are required if therapy and further basic investigations are to be conducted intelligently and fruitfully.

REFERENCES

1 ABBIE, A. A. (1934) *J. Anat.*, **68**, 433.
2 ALEXANDER, L. (1942) *Res. Publ. Ass. nerv. ment. Dis.*, **21**, 77.
3 COOPER, I. S. (1953) *Psychoanal. Quart.*, **27**, 317.
4 —— (1954) *Surg. Gynec. Obstet.*, **99**, 207.
5 MEYERS, R. (1942) *Res. Publ. Ass. nerv. ment. Dis.*, **21**, 602.
6 FENELON, F. (1950) *Rev. Neurol. Psychiat.*, **83**, 437.
7 GUIOT, G., and BRION, S. (1952) *Sem. Hôp. Paris*, **28**, 2095.
8 SPIEGEL, E. A., and WYCIS, H. T. (1954) *Arch. Neurol. Psychiat., Chicago*, **71**, 598.
9 NARABAYASHI, H., and OKUMA, T. (1953) *Proc. Japan Acad.*, **29**, 134.
10 HASSLER, R. (1938) *J. Psychol. [Neurol., Lpz.*, **48**, 387.
11 COOPER, I. S. (1956) *Science*, **119**, 417.
12 ——, and POLOUKHINE, N. (1955) *J. Amer. Ger. Soc.*, **3**, 839.
13 —— (1956) The Neurosurgical Alleviation of Parkinsonism. Springfield, Ill.
14 ——, and BRAVO, G. J. (1958) *J. Neurosurg.*, **15**, 244.
15 —— (1958) *Postgrad. Med.*, **24**, 153.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Section of Experimental Medicine and Therapeutics

President—M. L. ROSENHEIM, C.B.E., F.R.C.P.

Meeting
October 14, 1958

DISCUSSION ON WILSON'S DISEASE

Dr. A. G. Bearn (The Rockefeller Institute, New York, U.S.A.):

Genetic Aspects of Wilson's Disease

The genetic aspects of Wilson's disease can be considered from two main points of view. The first concerns the attempt to establish the exact mode of inheritance of Wilson's disease, and the second is an enquiry into the mechanism of the action of the abnormal gene. Although Kinnier Wilson (1912) considered the disease familial and not inherited, subsequent work has established beyond reasonable doubt that the disease is inherited in an autosomal recessive fashion (Matthews *et al.*, 1952; Bearn, 1953) in which the heterozygote, although clinically unaffected, may show some of the characteristic biochemical features of the disease (Bickel *et al.*, 1957; Bearn, 1957).

The collection of 30 sibships with Wilson's disease has enabled a genetical analysis to be carried out. A first-cousin consanguinity rate in the parents of patients with Wilson's disease of 0·37 was obtained, with a total consanguinity rate of 0·43. No parents of affected patients have been found to be suffering from overt Wilson's disease.

The ethnic background of 30 families with Wilson's disease was studied; 40% of these families were Jews who came from Central Europe, and 17% were Italians who came from Sicily or Southern Italy. It seems possible that many of the cases seen in New York City may have arisen from a relatively few mutations occurring in Sicily and in Central Europe. Mutations in populations where the breeding structure was less conducive to inbreeding diminished the likelihood of homozygosity for the abnormal gene.

Although the primary product of the Wilson's disease gene is not known, a relatively constant biochemical abnormality found in the disease is a diminution in the serum cæruloplasmin (Bickel *et al.*, 1957; Bearn, 1957; Scheinberg and Gitlin, 1952). In fact, a low cæruloplasmin has not been found in any neurological condition other than Wilson's disease. An investigation was carried out in an attempt to detect a biochemical abnormality in the parents of those afflicted who, of course, must be heterozygotes, and in unaffected siblings who have a 50% chance of being carriers. Scattered reports (Bearn, 1953; Bickel *et al.*, 1957) have suggested that occasionally the heterozygote may be detectable. Further studies have confirmed these observations, but the situation is expectedly complex. Some parents have an unequivocally diminished level of cæruloplasmin whereas others may be in the normal range. Asymptomatic siblings without Kayser-Fleischer rings with a low cæruloplasmin have now been observed by a number of investigators (Bickel *et al.*, 1957; Bearn, 1957; Scheinberg *et al.*, 1958). The mean concentration of serum cæruloplasmin in heterozygotes is probably lower than that of normal individuals but more data must be collected on this point. The fact that segregation into three groups is not distinct is again evidence that cæruloplasmin is unlikely to be the primary gene product. If the precise reaction regulated by the Wilson's disease gene were known with certainty, it would be considerably easier to detect the heterozygote with regularity.

The clinical variability of the disease and the wide scatter of serum cæruloplasmin levels suggests that the condition is probably not genetically homogeneous. There may be at least two types of Wilson's disease, one in which the metabolic block occurs at a level where a lowered cæruloplasmin accompanies the disease and

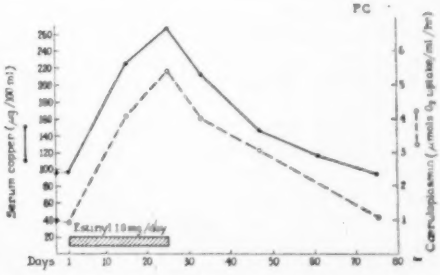

FIG. 1.—The effect of Estinyl on the serum cæruloplasmin of a patient with Wilson's disease.

another and rarer type in which the disease can exist with a normal level of serum cæruloplasmin. The concentration of serum cæruloplasmin can moreover be markedly elevated in normal subjects and in many patients with Wilson's disease by the administration of œstrogens, emphasizing, if this were needed, that alterations in the environment can modify an expression of the abnormal gene (Bickel *et al.*, 1957) (Fig. 1). It is possible that a tolerance test in which a rise of serum cæruloplasmin following the administration of œstrogens can be compared in normal subjects, patients with Wilson's disease, and heterozygotes, will more easily discriminate between the three groups.

REFERENCES

BEARN, A. G. (1953) *Amer. J. Med.*, **15,** 442.
—— (1957) *Amer. J. Med.*, **22,** 743.
BICKEL, H., NEALE, F. C., and HALL, G. (1957) *Quart. J. Med.*, **26,** 527.
MATTHEWS, W. B., MILNE, M. D., and BELL, M. (1952) *Quart. J. Med.*, **21,** 425.
SCHEINBERG, I. H., and GITLIN, D. (1952) *Science*, **116,** 484.
——, HARRIS, R. S., MORELL, A. G., and DUBIN, D. (1958) *Neurology*, Suppl. 1, **8,** 44.
WILSON, S. A. K. (1912) *Brain*, **34,** 295.

Professor J. N. Cumings (London):

The Treatment of Hepatolenticular Degeneration

Until 1948 no rational treatment was available for patients with hepatolenticular degeneration. Various symptomatic therapies have been used, as also have vitamin B_6 and cytochrome, while some physicians have given methionine, choline and even deoxycorticosterone.

During the late War, Peters and his colleagues (*see* Peters, 1951) developed a compound 2,3-dimercaptopropanol (BAL). McCance and Widdowson (1946) and Mandelbrote *et al.* (1948) demonstrated that BAL released copper from the body. Cumings (1948) suggested that this substance should be used for treating patients with hepatolenticular degeneration, and three years later the result of such treatment on 4 patients was published (Cumings, 1951). Denny-Brown and Porter (1951) in the same year also reviewed their results following the treatment of 5 cases.

Since then many other patients have been treated along similar lines but other drugs have also been used, such as Versene (EDTA) and more recently penicillamine introduced by Walshe (1956*a*), and these and other recent methods of treatment will be discussed.

An exchange or exsanguination blood transfusion has been attempted by Alajouanine *et al.* (1955) but the patient died. This therapy is probably useless but I must add that Alajouanine's patient also received BAL.

Bickel *et al.* (1956) have attempted to show that by intravenous injections of cæruloplasmin the absence of this substance could be overcome. It is true that the blood copper and cæruloplasmin contents of their cases rose. Dr. Curzon (*see* p. 64) states that cæruloplasmin, as so far prepared, is at best only 90% pure, and that being a protein it might well produce unfavourable reactions. But the 3 cases treated by Bickel *et al.* (1956) failed to show clinical improvement and I cannot find, as yet, any evidence from any source to suggest that a patient may be significantly improved by this mode of therapy.

Cortisone has been tried without success, patients I have seen showing neither increased output of urinary copper nor clinical improvement.

Molybdenum affects copper metabolism in animals in addition to causing demyelination in the nervous system (Dick and Bull, 1945). Treatment by this substance has been tried by Bickel *et al.* (1957) in 4 patients. A well-marked increase of urinary copper resulted but without clinical improvement. I have examined the excretion of urinary copper in one patient given molybdenum and the result in so far as the patient was concerned was no different from the cases Hall treated (Table I).

Versene (EDTA) is well known as a remover from the body of heavy metals and has been used extensively in lead poisoning. In this country, Bickel *et al.* (1957) have treated 6 patients with EDTA using the oral route in all, the intravenous route in 3, while 2 patients were given intramuscular Versene. 3 of the 6 died, and only 1 of the 6 received EDTA with no other drug. Clinically the results were not really encouraging but 8 of the 12 cases seen by these workers died, so that other forms of therapy appeared equally ineffective. Nevertheless they recommended intramuscular or intravenous injections of EDTA, for they found that oral Versene failed in 3 out of 6 cases to cause any increase in urinary copper. I personally have a record of only 1 patient who was given oral EDTA, without obvious benefit, and with no increased excretion of copper in the urine (Table I).

Wintrobe *et al.* (1954) found an increased absorption of copper from the alimentary tract in patients with hepatolenticular degeneration and that this could be prevented by the oral administration of potassium sulphide. Many workers in North America and in England now follow this practice and for the past two to three years I have given all my patients 20 mg. of potassium sulphide in a capsule three times a day. This is taken permanently and the patient

is also advised to reduce the intake of articles of food known to contain large amounts of copper. Irrespective of whatever other form of therapy I might advise, I would retain the administration of potassium sulphide.

There now remain two main forms of therapy, BAL and penicillamine, and these will be discussed together. Some difficulty exists for while some patients have been treated by BAL for up to eight years, experience with penicillamine is limited in time, hence a true and accurate comparison is not yet possible.

Walshe (1956*b*) has said that penicillamine produces a greater excretion of copper than does BAL. Table I shows the effect of various forms of therapy which have been administered to patients seen personally, and it can be seen that Walshe's statement is correct. The patients examined by Walshe were in general those who had previously received BAL, and included some of the patients treated at Queen Square and who returned there for more BAL. Table I therefore includes the results of urinary copper excretion in a patient (M. Le) who was given penicillamine before any other form of therapy, even though she was given BAL later.

TABLE I.—URINARY COPPER EXCRETION AFTER VARIOUS FORMS OF THERAPY

Case	Sex	Age	Treatment	Copper output on days before treatment	Copper output on days during treatment
				μg./day	μg./day
C. L.	F.	15	Molybdenum	690	1,911
				560	1,097
				580	1,890
J. G.	M.	45	Oral Versene	472	744
				726	461
				602	821
J. G.	M.	45	BAL	351	617
				430	806
				384	795
J. G.	M.	45	Penicillamine	596	1,178
				329	1,134
				700	1,482
M. Le	F.	25	Penicillamine	250	966
				353	1,282

Penicillamine is given orally, 0·5 to 1·5 grams daily in divided doses, and gives rise to extremely few toxic effects. BAL is given by injection and toxic reactions may occur. However, in 20 patients treated with BAL, I have seen no marked toxic reactions during the first three or four courses of BAL, but in 1 patient a serious degree of reaction occurred to the usual dose after about two years, but this has been overcome. Penicillamine is an easier substance to administer and undoubtedly gives rise to a considerable removal of copper from some part of the body, for in 1 patient, whose urine has only just been examined, the output of copper rose from about 300 μg. a day to just over 3,000 μg. a day. However, at present a week's treatment with penicillamine costs nearly £10 as compared to £1 12s. 0d. for a week's treatment with BAL.

Does a patient treated by either method improve? Some 20 patients have now been given BAL and have been followed up for six months or more, while half have been followed up for more than two years. Until a few weeks ago no deaths had occurred but contact had been lost with 4 of these patients. Just recently 1 patient developed œsophageal varices and a short-circuit operation was performed. After an initial recovery this patient died from liver insufficiency and with a well-marked cirrhosis of the liver. The results that have been obtained are shown in Table II (*see also* Cumings, 1957).

TABLE II.—PATIENTS TREATED BY BAL

Case	Sex	Age when first seen	Clinical result of treatment	Follow-up period	
				years	
18550	M.	27	Nil → ±	5	Still under treatment
21191	F.	21	+ +	8	Still under treatment
F. K.	M.	26	+ (H)	3½	Contact lost
43931	M.	24	+ (S)	3½	Still under treatment
C. La	F.	16	+ ± (H)	2½	Still under treatment
S. Fi	F.	16	+ ±	2	Still well
60861	F.	19	+ + (H)	2½	Died September 1958
J. G.	M.	45	+	2½	Still under treatment
62389	F.	30	+ +	2	Still under treatment
W. Cr	M.	23	+ +	2	Still under treatment
16399	M.	36	+	1	Contact lost
23815	M.	24	+ +	1	Contact lost } Returned
63835	M.	20	Nil	½	Contact lost } to Iran
63359	F.	18	+	1½	Still well
L. Fr.	F.	13	+	1	Still under treatment
D. B.	M.	18	+	1	Still under treatment
70379	M.	18	+	1½	Still under treatment
D. Cl	M.	17	+	½	Still under treatment
M. Le	F.	25	+ +	½	Still under treatment
E. H.	M.	36	±	½	Still under treatment

H = Hepatic dysfunction. ± Very slight improvement.
S = Schizophrenia. + Some improvement.
+ + Marked improvement.

Originally BAL was given for a week and this course was repeated after one week's rest. 2·5 mg. BAL per kg. of body weight was given twice a day. Recently patients have been given 100 mg. BAL once a week for by so doing the patient has not needed to stay in hospital.

I have little doubt but that BAL benefits the patient clinically. Can the same be said for penicillamine? From the short experience I have had lasting now for perhaps six months, I have seen some slight improvement. Some patients have maintained this very slight improvement on penicillamine and potassium sulphide, but one patient given penicillamine as the first form of therapy had to receive BAL before demonstrating clinical improvement. One wonders what the differences between the results mean;

TABLE III.—SERUM COPPER AND OXIDASE ACTIVITY LEVELS BEFORE AND AFTER TREATMENT

Case	43931		62389		21191		60861	
	Cu	Oxidase	Cu	Oxidase	Cu	Oxidase	Cu	Oxidase
Before treatment	65	0	48	8	70		63	34
At varying times after treatment	57	6	42	0	57	0	62	34
	63	0	47	0	40	0	67	29
	73	5	37	0			70	42

Copper in μg./100 ml. Oxidase activity in μL O_2/ml./hour.

could it be that penicillamine removes copper better from the liver than from the brain? Three patients, despite clinical improvement on BAL, showed increasing evidences of liver cirrhosis. Should patients receive both penicillamine and BAL? This is pure speculation. If it were true, should patients be given oral penicillamine in 0·5 gram doses daily, together with 100 mg. BAL once or twice weekly?

Lastly, what effect does BAL, and possibly penicillamine, have on the biochemical abnormalities found in the blood? Although most of the patients recorded in Table II have been repeatedly examined for levels of blood copper and of copper oxidase activity, no biochemical improvement has been found in any, even after three years of treatment. Some of the results that have been found are recorded in Table III.

Nevertheless, one would not expect blood changes to be found if these copper abnormalities were essential features of a disease due to some inborn metabolic error. It should be mentioned that the examination of the liver of the patient who died contained only 20·3 mg. of copper per 100 grams dry tissue, which is no higher than that found in cirrhosis and considerably lower than the amount found in the livers from untreated cases of this disorder (Cumings, 1948). Therapy had therefore reduced the copper content of the liver even though not altering the histological abnormality.

REFERENCES

ALAJOUANINE, TH., BERTRAND, I., BOUDIN, G., and PÉPIN, B. (1955) *Rev. Neurol.*, **93,** 701.

BICKEL, H., NEALE, F. C., and HALL, G. (1957) *Quart. J. Med.*, **26,** 527.

——, SCHULTZE, H. E., GRÜTER, W., and GÖLLNER, I. (1956) *Klin. Wschr.*, **34,** 961.

CUMINGS, J. N. (1948) *Brain*, **71,** 410.

—— (1951) *Brain*, **74,** 10.

—— (1957) I *Congr. int. Sci. Neurol.*, **1,** 172.

DENNY-BROWN, D., and PORTER, H. (1951) *New Engl. J. Med.*, **245,** 917.

DICK, A. T., and BULL, L. B. (1945) *Aust. vet. J.*, **21,** 70.

MCCANCE, R. A., and WIDDOWSON, E. M. (1946) *Nature, Lond.*, **157,** 837.

MANDELBROTE, B. M., STANIER, M. W., THOMPSON, R. H. S., and THRUSTON, M. N. (1948) *Brain*, **71,** 212.

PETERS, R. A. (1951) *Edinb. med. J.*, **58,** 197.

WALSHE, J. M. (1956*a*) *Lancet*, i, 25.

—— (1956*b*) *Amer. J. Med.*, **21,** 487.

WINTROBE, M. M., CARTWRIGHT, G. E., HODGES, R. E., GUBLER, C. J., MAHONEY, J. P., DAUM, K., and BEAN, W. B. (1954) *Trans. Ass. Amer. Phycns.*, **67,** 232.

Dr. G. Curzon (London):

The Chemistry and Biochemistry of Cæruloplasmin

Almost all of the copper in human plasma is bound to a specific protein. Holmberg and Laurell (1948) first isolated this cuproprotein from plasma and because of its blue colour they called it cæruloplasmin. It has a molecular weight of about 151,000 and 0·34% of copper which corresponds to 8 atoms of copper per molecule. Purified cæruloplasmin runs on electrophoresis as an α_2 globulin, though by direct salting out of plasma some association of copper with fractions of other mobilities has been shown (Thompson and Watson, 1949; Cumings *et al.*, 1955). Like a number of other cuproproteins, cæruloplasmin behaves as an enzyme, having oxidase activity (Holmberg and Laurell, 1951).

Between Holmberg and Laurell's final paper (1951) and 1957 there was little published work on cæruloplasmin. This has partly been due to difficulties in obtaining reasonably pure material in quantity. Mr. L. Valet and I have worked out a method which at present gives cæruloplasmin of 90% purity and should be capable of application on a fairly large scale. The G_2 fraction of plasma is used as starting material. This is available in this country as a by-product in the preparation of fibrinogen, gamma-globulin, &c. The method involves conventional techniques of protein separation with ether, followed by fractionation on an anion exchange cellulose column.

I shall discuss three topics: first, the significance of cæruloplasmin in Wilson's disease, second, the nature of copper binding in cæruloplasmin, and finally, its properties as an enzyme.

Cæruloplasmin in Wilson's Disease

In Wilson's disease, cæruloplasmin in the plasma is much decreased or essentially absent (Scheinberg and Gitlin, 1952). Abnormally high amounts of copper are found in the brain, liver (Cumings, 1948) kidneys and cornea. Though the total plasma copper is decreased the amount of weakly bound, direct reacting non-cæruloplasmin copper is raised (Scheinberg, 1956). It seems probable that the clinical manifestations of the disease are related to the defect in cæruloplasmin synthesis and subsequent availability of copper for deposition in the tissues. Zimdahl *et al.* (1953) found increased absorption of copper from the alimentary tract. So far there has been no adequate explanation linking this up with defective cæruloplasmin synthesis. Scheinberg and Morell (1957) have, however, suggested that perhaps in normal subjects loosely bound copper in the intestinal plasma, derived from local cæruloplasmin metabolism, would oppose diffusion of ionic copper from the lumen into the plasma and that this mechanism would no longer operate in Wilson's disease.

Porter and Folch (1957) have shown that part of the excess copper present in the brains of subjects with Wilson's disease is in a protein-bound form which is not found to an appreciable extent in normal brain. Also Uzman and his co-workers (1956) claim that the large amounts of copper present in cirrhotic livers of subjects with Wilson's disease are bound to an abnormal protein with a specially high affinity for copper. They do not, however, mention if this high affinity is specially found in cirrhotic livers of subjects with Wilson's disease or in cirrhotic livers in general. Chalmers *et al.* (1957) suggest that the amino-aciduria and peptiduria often associated with Wilson's disease are the primary biochemical defects. Large amounts of copper are excreted bound to peptides and are thus not available for cæruloplasmin synthesis. There is strong evidence against this, as cases of Wilson's disease have been described in which, though cæruloplasmin levels are low, there is no abnormal amino-aciduria (Cooper *et al.*, 1950). The latter is thus more probably related to liver kidney damage caused by abnormally high amounts of circulating direct reacting copper.

Copper Binding in Cæruloplasmin

Earl and his co-workers (1954) showed that when ^{64}Cu is fed to normal human subjects it is bound first mainly to the serum albumin and is later transferred to the globulin fraction, presumably being incorporated in newly synthesized cæruloplasmin. The transfer to globulin does not occur in subjects with Wilson's disease. Though copper can be shown *in vitro* to bind to some extent to albumin and other proteins, it is particularly strongly bound within cæruloplasmin at a pH range around neutrality. It is of interest to compare some of the properties of cæruloplasmin with those of the looser albumin-copper complex (Table I). Whereas copper dialyses away from albumin with difficulty and incompletely, cæruloplasmin copper is completely non-dialysable around neutrality. Copper is removed from the albumin-copper complex on a ZeoCarb 225 column, whereas cæruloplasmin copper is unaffected. Diethyl-dithiocarbamate reacts with ionic copper to give a yellow complex extractable by organic solvents. Albumin-copper gives a yellow complex which is not extractable. Cæruloplasmin copper does not react at all.

Table I.—Comparison of Free Copper, Albumin-bound Copper and Cæruloplasmin Copper

	Free copper	*Albumin bound copper*	*Cæruloplasmin copper*
Dialysis	Free	Difficult	Non-dialysable
Copper removal by ZeoCarb 225	+	+	–
Reaction with diethyl-dithio-carbamate	+	+	–
Extraction of diethyl-dithio-carbamate reaction product	+	–	–

Another point indicating a special kind of binding of copper in cæruloplasmin is the great intensity of the colour of cæruloplasmin compared with that of artificial protein-copper complexes.

After protein denaturation by heat, cæruloplasmin copper reacts directly with diethyl-dithio-carbamate. This suggests that the strong binding of copper to the apo-protein is not due to any unusual component of the protein, but to the particular arrangement of the peptide chains resulting in juxtaposition of the more strongly copper-binding amino acid residues. Most amino acids bind copper with similar avidities but histidine and cysteine bind it more strongly. On denaturation the general disorientation results in loss of copper-binding power. A similar interpretation was made by Fraenkel-Conrat (1950) of the effects of denaturation on the iron binding capacity of conalbumin.

Fig. 1 shows how this kind of structure may result in very powerful copper binding. The cupric ion can co-ordinate strongly with 4 coplanar groups and also, but much more rarely, with 2 extra more distant groups at right angles. Co-ordinate links between cupric ion

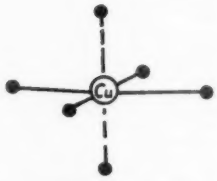

FIG. 1A.—Arrangement of atoms in cupric complexes.

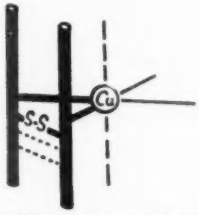

FIG. 1B.—Possible arrangement in cæruloplasmin.

and nitrogen are particularly readily formed. Thus structures can be envisaged in which each copper atom provides a strong cross link between side chains of 4 parallel peptide chains. If the structure was further stabilized by hydrogen bonds and sulphur bridges between the chains, a polydentate copper-protein chelate would be formed in which a number of bonds between copper and amino acid residues would have to be broken simultaneously for copper to be released. In Fig. 1 only 2 peptide chains are indicated for the sake of simplicity. Structures of this kind would be rather difficult to denature because of copper cross-links between chains. It is of interest that methods of purification of cæruloplasmin tend to involve a stage in which contaminant protein is denatured and copper protein left intact. The rather slow chymotryptic degradation of cæruloplasmin also suggests resistance to denaturation, as this is usually a necessary preliminary for proteolytic breakdown.

There are some indications of a relationship between cæruloplasmin, the liver cuproprotein hepatocuprein and the hæmocuprein isolated from whole blood by Mann and Keilin (1939). Hæmocuprein has a molecular weight a quarter that of cæruloplasmin but the same percentage of copper, giving two atoms of copper per molecule. Like cæruloplasmin they do not react directly with diethyl-dithio-carbamate. They have not so far been shown to have any enzymic activity. The arithmetical relationship between these proteins may be entirely coincidental or it may be that hæmocuprein is merely an artifact, but it suggests that the cæruloplasmin molecule consists of 4 sub-units which are related in some way to hepatocuprein and hæmocuprein. It would be of interest if a defect in hepatocuprein and hæmocuprein synthesis as well as cæruloplasmin synthesis could be demonstrated in hepatolenticular degeneration. Other information indicating a simple arithmetical relationship in the cæruloplasmin molecule is provided by a recent paper by Scheinberg and Morell (1957). They showed that if cæruloplasmin is incubated with ^{64}Cu and ascorbic acid, half only of the cæruloplasmin copper exchanges with the isotope. They suggest that during the oxidation of ascorbic acid, cæruloplasmin copper shuttles between the strongly bound cupric state and a more weakly bound cuprous state which is capable of exchange with ionic copper and that half only of the protein-bound copper is involved. Other evidence of an accessibility of 4 out of the 8 cæruloplasmin copper atoms is given by chymotryptic digestion of cæruloplasmin (Table II)

TABLE II.—NON-DIALYSABLE COPPER IN CHYMOTRYPTIC DIGESTS OF CÆRULOPLASMIN (CURZON, 1957)

Digestion Exp. No.	Cæruloplasmin (mg.)	Chymotrypsin (mg.)	Digestion time (hr.)	Per cent copper non-dialysable after digestion
1	20·1	3	22	56
2	7·0	1	22	52
3	9·0	3	22	49
4	11·8	2	65	55

(Curzon, 1957). One half only of the copper is rendered dialysable, similar results being obtained under a variety of conditions. This is probably not simply due to equilibrium between various reaction products, as in experiment No. 4 after sixty-five hours' digestion an aliquot of the non-dialysable material was taken, the original amount of chymotrypsin doubled and digestion allowed to proceed for a further twenty-three hours. This resulted in no further liberation of copper from the non-dialysable material. Thus cæruloplasmin appears to possess a resistant core containing 4 of the original 8 copper atoms.

CÆRULOPLASMIN AS AN ENZYME

Holmberg and Laurell showed that *in vitro* cæruloplasmin acts as an enzyme oxidizing a variety of polyhydroxylic and polyamine substrates. These include paraphenylene diamine, hydroquinone, catechol, pyrogallol, adrenalin and ascorbic acid. More recently, 5-hydroxytryptamine (Porter *et al.*, 1957) and 5-hydroxyindole acetic acid (Curzon, unpublished) have also been shown to be substrates. In general, activity is determined using para-

phenylene diamine or its NN-dimethyl derivative as substrates and measuring either uptake of oxygen or optical density of the coloured reaction product. Optimal pH is about 5·5 for most substrates and activity is inhibited by cyanide and azide, presumably because of their strong avidity towards copper. Detailed study of the effects of copper complexing inhibitors may provide information on the way copper is involved in the enzymic action and indirectly on the binding of copper to the apo-protein. It is of interest to note that Holmberg and Laurell found no inhibition with carbon monoxide, and I have not been able to show inhibition with diquinolyl and dimethyl-phenanthroline. These substances combine with copper in the cuprous state and it is a little surprising that they have no effect if cæruloplasmin copper does indeed shuttle between the cupric and cuprous states during action on substrate. Ethylene diamine tetracetic acid (Versene) acts as an inhibitor though evidence indicates that copper binding is probably not involved (Curzon, unpublished).

Among substrates of cæruloplasmin *in vitro* are two of particular interest, adrenaline and 5-hydroxytryptamine. Adrenaline is oxidized to a complex mixture including adrenochrome. 5-hydroxytryptamine is oxidized by cæruloplasmin to a mixture of products some of which are themselves indolic. It is important to know if cæruloplasmin oxidizes these substances under physiological conditions and it may be possible to obtain some information on this, using subjects with Wilson's disease. In Fig. 2

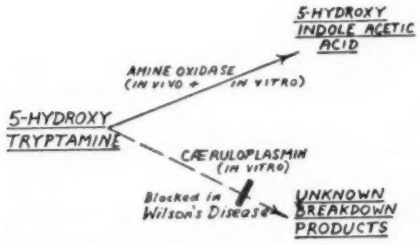

FIG. 2.—Cæruloplasmin and 5-hydroxytryptamine.

5-hydroxytryptamine metabolism is taken as an example, though a similar argument can be used for adrenaline metabolism. The known *in vivo* pathway of 5-hydroxytryptamine metabolism is by amine oxidase to 5-hydroxyindole acetic acid, which is excreted. If the cæruloplasmin pathway is quantitatively significant, then it would be expected that subjects with little or no cæruloplasmin would metabolise more 5-hydroxytryptamine on the amine oxidase pathway and thus excrete more 5-hydroxyindole acetic acid. Determinations on a small group of subjects with hepatolenticular degeneration so far indicate that 5-hydroxyindole acetic acid excretion is within the normal range. However, even if the cæruloplasmin pathway is only responsible for a small fraction of 5-hydroxytryptamine metabolism this could be important as among the possible metabolites are substances which could be quite active. It is, however, unknown whether cæruloplasmin acts as an enzyme *in vivo* at all. Activity at physiological pH tends to be low though optimal pH does vary to some extent with substrate and ionic environment. It may be that the physiological function of cæruloplasmin is related to copper detoxication and that the *in vitro* enzyme activity does not occur under physiological conditions, though it does provide one with a convenient method for its determination and study.

REFERENCES

CHALMERS, T. C., IBER, F. L., and UZMAN, L. L. (1957) *New Engl. J. Med.*, **256,** 235.

COOPER, A. M., ECKHARDT, R. D., FALOON, W. W., and DAVIDSON, C. S. (1950) *J. clin. Invest.*, **29,** 265.

CUMINGS, J. N. (1948) *Brain*, **71,** 212.

——, GOODWIN, H. J., and EARL, C. J. (1955) *J. clin. Path.*, **8,** 69.

CURZON, G. (1957) *Nature, Lond.*, **181,** 115.

EARL, C. J., MOULTON, M., and SELVERSTONE, B. (1954) *Amer. J. Med.*, **17,** 205.

FRAENKEL-CONRAT, H. (1950) *Arch. Biochem.*, **28,** 452.

HOLMBERG, C. G., and LAURELL, C. B. (1948) *Acta chem. scand.*, **2,** 550.

——, —— (1951) *Acta chem. scand.*, **5,** 476.

MANN, T., and KEILIN, D. (1939) *Proc. roy. Soc.*, Ser. B., **126,** 303.

PORTER, C. C., TITUS, D. C., SANDERS, B. E., and SMITH, E. V. C. (1957) *Science*, **126,** 1014.

PORTER, H., and FOLCH, J. (1957) *Arch. Neurol. Psychiat., Chicago*, **77,** 8.

SCHEINBERG, I. H. (1956) *In:* Neurochemistry. Edited by S. R. Korey and J. I. Nurnberg. London; p. 52.

——, and GITLIN, D. (1952) *Science*, **116,** 484.

——, and MORELL, A. G. (1957) *J. clin. Invest.*, **36,** 1193.

THOMPSON, R. H. S., and WATSON, D. (1949) *J. clin. Path.*, **2,** 193.

UZMAN, L. L., IBER, F. L., and CHALMERS, T. C. (1956) *Amer. J. med. Sci.*, **231,** 511.

ZIMDAHL, W. T., HYMAN, I., and COOK, D. (1953) *Neurology*, **3,** 569.

BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

Bensaude (R.). Rectoscopie, sigmoïdoscopie. 3rd. ed. pp. 267. Paris: Masson. 1956.

Bramwell (J. C.). Practice, teaching, and research. The Harveian Oration of 1956. pp. 20. London. 1956.

Brodie (Sir Benjamin Collins). Notes of lectures on the theory and practice of surgery delivered by B. C. Brodie, F.R.S., during the season 1822–1823 at his theatre: Great Windmill Street, London. Manuscript. Vol. I. pp. 361. 1822–23.

Buchthal (F.), and Kaiser (E.). The rheology of the cross striated muscle fibre. pp. 318. Copenhagen. 1951.

Buschke (A.), and Gumpert (M.), eds. Geschlechtskrankheiten bei Kindern. pp. 108. Berlin: Springer. 1926.

Charles (Sir John A.). The contrivance of collegiation. The Harveian Oration of 1955. pp. 24. London. 1955.

Christensen (O. E.). Om tuberkelbacillers resistensudvikling under behandling af lungetuberkulose med streptomycin, PAS, Tb I og med nogle kombinationer af disse stoffer: en klinisk biologisk studie. pp. 301. Copenhagen: Dansk Videnskabs Forlag. 1954.

Congresses. Cancer. VII International cancer congress, London, July 1958. Abstracts of papers. pp. 417. London. 1958.

Congresses. Microbiology. VII International congress Stockholm, August 1958. Program and abstracts of papers. 2 vols. Stockholm: Almqvist and Wiksell. 1958.

Engel (S.), and Baum (M.). De verzorging van zuigeling en kleuter. pp. 236. Amsterdam: Scheltema and Holkema. *c.* 1944.

Fleurent (H.). L'art et la médecine au Musée de Colmar. pp. 32. Colmar: Société Schongauer. 1928.

Fournier (A.). A propos de la prophylaxie et du traitement de l'hérédo-syphilis. pp. 136 Paris: Delagrave. 1910.

Helwig (B.). Moderne Arzneimittel. pp. 301. Stuttgart: Wissenschaftliche Verlagsgeselt. 1958.

Honcke (P.). Investigations on the structure and function of living, isolated, cross striated muscle fibres of animals. pp. 230. Aarhus. 1947.

Hunter (D.). Harvey and his contemporaries. The Harveian Oration of 1957. pp. 28. London. 1957.

Hutinel (V.). Le terrain hérédo-syphilitique. pp. 455. Paris: Masson. 1926.

Keyes (N. B.). Ben Franklin: an affectionate portrait. pp. 318. Kingswood, Surrey: World's Work. 1956.

Lilly (Eli), and Co. Diabetes mellitus: Methods of dietetic management and the use of insulin preparations. 4th ed. pp. 163. Indianapolis: Lilly and Co. 1951.

Ludovici (A. M.). The truth about childbirth. pp. 294. London: Kegan Paul. 1937.

McIntire (R. T.). Twelve years with Roosevelt. pp. 244. London: Putnam. 12s. 6d. 1948.

Mattea (E.). Tumori della vescica nei lavoratori delle amine aromatiche. pp. 103. Milan: Ambrosiana. 1958.

Meneghetti (E.). Farmacologia. 9th ed. 2 vols. Padua: Cedam. 1958.

Mitchell (G. A. G.). Anatomy of the autonomic nervous system. pp. 356. Edinburgh and London: Livingstone. 1953.

Morowoka (T.), et al. Histology of the autonomic nervous system as revealed by the nonmicrotomic splitting method. Fukuoka. 1958.

Moynihan (Sir Berkeley G. A.). Zwei Vorlesungen über das Magen- und Duodenalgeschwür. pp. 40. Berlin: Springer. 1925.

Olivier (C.). Radio-diagnostic des occlusions intestinales aiguës. pp. 258. Paris: Masson. 1955.

Pfizer, Ltd. The Pasteur fermentation centennial 1857–1957. pp. 207. New York: Pfizer. 1958.

Pollard (B.). The introductory address in the Faculty of Medicine of University College, London, October 1893. pp. 30. London: Bale. 1893.

Progress in Clinical Endocrinology. Soskin (S.), ed. Vol. 1. London. 1950.

Ravaut (P.). Une nouvelle syphilis nerveuse: ses formes cliniquement inapparentes. pp. 196. Paris: Masson. 1934.

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Meeting
October 9, 1958

DISCUSSION ON THE TRABECULAR STRUCTURE IN RELATION TO THE PROBLEM OF GLAUCOMA

Professor Norman Ashton (Institute of Ophthalmology, London):

In simple glaucoma, with which we are particularly concerned in this discussion, it is now certain that there is an impediment to aqueous outflow, but as yet the exact site and nature of the obstruction has not been conclusively demonstrated. Some would incriminate the structures of the trabeculæ and others the outflow channels through the sclera, but it is important to remember that there is no theoretical reason why the obstruction should be as selectively located for it may equally well result from a summation of minimal changes throughout the entire pathway of exit, and these may not be of a wholly structural kind. Nor can one suppose that all cases of simple glaucoma need be identical, for the emphasis of the pathology might vary as between the trabecular meshwork and the scleral outlets.

At the Institute of Ophthalmology we have for many years been trying to establish exact criteria of normality in the micro-anatomy of the outflow pathways in order to recognize significant deviations, if such exist, in glaucomatous eyes. The problem is not an easy one. The techniques available so often provide inconclusive evidence and the only human material available for laboratory study is, of course, subject to post-mortem degeneration and may grossly misrepresent the conditions pertaining in living tissue. Even when artifact can be excluded in the microscopical study of glaucoma the question remains whether the changes are causative or consequential.

As regards the normal meshwork, the chief remaining problem is the role of mucopolysaccharide both in trabecular structure and function. Since the discovery of Bárány (1953) that the resistance of the outflow barrier of the animal eye may be decreased by the action of hyaluronidase several workers have tried to demonstrate a hyaluronidase-sensitive mucopolysaccharide within the uveal meshwork of animals and man. A coating substance apparently sensitive to hyaluronidase has in fact been demonstrated in the trabecular meshwork of cattle, sheep and rabbits (Berggren and Vrabec, 1957; Brini, 1957) and on the corneal endothelium of owls (Bárány *et al.*, 1957).

Metachromasia—a characteristic property of acid mucopolysaccharides—has been demonstrated between the trabeculæ in the sheep's eye (Vrabec, 1957*a*) and within the trabeculæ of the human eye (Ashton *et al.*, 1956). However, the belief that a hyaluronidase-sensitive mucopolysaccharide exists in the human uveo-scleral meshwork rests mainly upon the reports of Brini (1956, 1957) who, by using toluidine and alcian blue, found such a substance *within* the trabeculæ, and that of Zimmerman (1957) who, using a colloidal iron method, found it *between* the trabeculæ. These reports, however, cannot be regarded as conclusive for not only are they in conflict but are otherwise subject to criticism. Unfortunately Zimmerman did not provide the details of his experiments or indicate the number of eyes in which this substance was found, and it is disappointing that in an examination of 50 freshly enucleated eyes we have been completely unable to confirm his findings.

Brini used unphysiological concentrations of hyaluronidase (as he pointed out) and a much longer period of exposure to the enzyme than would justify an analogy with the perfusion experiments of Bárány. No histochemical stain is in fact entirely specific for mucopolysaccharides, and the specificity of hyaluronidase is seriously impaired by its possible contamination with proteolytic or other enzymes, which would be particularly important after long periods of incubation. Furthermore, the stainable groups within the tissues may be masked by the attachment of protein or other substances in the enzyme extract (Benditt and French, 1953), providing falsely positive results. Finally the addition of hyaluronidase to fluid in perfusion studies on human eyes has provided much less striking effects than those found in animal eyes (Pedler, 1956; François, Rabaey and Neetens, 1956; Peter *et al.*, 1957).

In my view, neither microradiography (François, Neetens and Collette, 1956) nor the replica technique (Vrabec, 1957*b*) seems sufficiently delicate to provide wholly reliable information. The fact that hyaluronidase cannot be detected

in aqueous humour—or indeed in the iris, ciliary body or cornea (Bárány and Woodin, 1955; Langley and McCulloch, 1958)—adds little to the solution of the problem.

Although it is undoubtedly true that mucopolysaccharide stains are positive in all the tissues of the anterior segment, we have found no particular concentration of this substance in the trabecular region. It remains possible of course that it exists in the living eye and rapidly disappears at death. I think, therefore, that it is still an open question whether hyaluronic acid exists in the human trabecular meshwork or not, and we have no direct evidence that such a substance is concerned in the control of either normal or abnormal aqueous outflow in man.

Turning now to consider the pathological changes in the aqueous pathway which have been considered of importance in simple glaucoma, we should first note that Teng and his colleagues (Teng *et al.*, 1955; Teng *et al.*, 1957) recently reported an extensive histological study in which degenerative changes in the trabecular region were noted as features of the ageing eye, and these were particularly severe in 4 cases of wide-angle glaucoma. The changes consisted of fragmentation of the collagen, break-up of elastic fibres, proliferation of endothelial cells extending into the collector channels, and adhesions in Schlemm's canal. Whether this widespread degeneration is of ætiological significance in simple glaucoma is uncertain, however, for their specimens were obtained from an eye bank and had been in saline for some days, while their 4 cases are doubtfully admissible as true examples of simple glaucoma. My colleagues and I (Ashton *et al.*, 1956) have recently shown how artifact and post-mortem autolysis can complicate this question. For instance, we found so-called canal "adhesions" in 25% of our sections irrespective of age of the subject, and I am quite certain from the examination of many degenerate eyes and particularly of 20 eyes stored in saline for several days, that all the angle changes described by Teng and others can arise from post-mortem autolysis. Judging from their illustrations and from the actual sections which I have examined I very much doubt whether there is any true endothelial proliferation. Some of the appearances are due to endothelial vacuolation; others to cellular infiltration or to cellular debris, and the apparent growth of endothelial cells into the collector channels results from prolapse of degenerate trabecular tissue into these openings. Indeed it is questionable whether proliferation of the endothelial cells of the human trabecular meshwork ever occurs, for they rapidly undergo hydropic degeneration when injured.

These post-mortem degenerations, however, are instructive for they clearly demonstrate that at least one type of trabecular degeneration—albeit post-mortem—may result in collapse of the trabecular meshwork with loss of lamellar alignment, which leads to obliteration of Schlemm's canal and possibly to a cellular occlusion of the collector channels. Hence the work of Teng and his co-workers cannot be dismissed simply as post-mortem artifact for it may well be that the changes we seek in glaucoma are of a closely related kind. Unless perfectly normal trabeculæ are found in early cases of simple wide-angle glaucoma, it is almost impossible in histological material to disentangle post-mortem from pathological changes. Here again, therefore, I think the role of trabecular pathology in simple glaucoma still remains an open question.

Considering now the collector channels and intrascleral vessels as a possible site of obstruction, it was recently pointed out (Ashton, 1955) that the most likely site as judged from casts and injected specimens was in the outer sclera, immediately before the intrascleral channels pour their contents into the episcleral vessels, and it was suggested that they may possibly become obliterated by ageing changes in the sclera.

About the same time Dvorak-Theobald and Kirk (1956) came to similar conclusions from a histological study of cases of chronic simple glaucoma. Subsequently I have shown by injecting Schlemm's canal with Indian ink that the collector channels in long-standing cases of glaucoma may in fact be markedly attenuated, but unfortunately one cannot say whether this is the cause or the result of the raised intra-ocular tension—a fact which must constantly be borne in mind in theorizing upon such evidence—so that here again our knowledge is inconclusive.

Microscopical changes in a case of early simple glaucoma.—Over the last few years I have, through the kind co-operation of Mr. M. J. Gilkes and Mr. Redmond Smith, obtained eyes from post-mortem cases who in life had attended the Glaucoma Clinic. Unfortunately the first 5 cases, for various reasons, were not completely admissible as perfect examples of simple glaucoma. A few weeks ago, however, the eyes from such a case became available. The full clinical history will be detailed elsewhere; the patient was a male aged 68 with early bilateral glaucoma showing typical arcuate scotomata,

cupped discs, raised tension, moderately deep open angles and impaired outflow. The posterior segment of the *left eye* (the more severely affected) was sectioned to show the cupped disc, the anterior segment was cut radially and Schlemm's canal injected directly with Indian ink, which flowed around the canal perfectly, there being *no evidence of adhesions* or *other obstructions*. The ink flowed easily into the episcleral and conjunctival vessels indicating a free communication via the intrascleral channels, but filling was deficient at 6 o'clock. The specimen was then cleared by the Spalteholz technique and re-examined.

After removal of the superficial vessels, no abnormality could be detected in the size or number of the collector channels (at least 18 could be counted), and although there was some attenuation of the intrascleral channels as compared with a normal specimen—one large outlet at 6 o'clock for instance ended blindly in the sclera—there appeared to be a considerable number of patent communications between the canal and episcleral vessels.

It is difficult to decide on this evidence alone whether these remaining patent channels were likely to have been sufficient to provide an adequate outflow, but it is interesting to recall that Ascher and Spurgeon (1949) estimated mathematically that obstruction of even a few of the larger outlets would very greatly increase the resistance to flow of the aqueous humour.

Six hundred serial sections from a segment of the *right eye* have so far been examined. In none of the sections was there any evidence in the trabecular meshwork of sclerosis, endothelial cell proliferation or an abnormal mucopolysaccharide content. In the majority of the sections, the trabecular fibres, the arrangement of the meshwork, and the appearances of the canal were completely normal, while in other areas the meshwork was collapsed and the canal obliterated, but no true adhesions were seen. In these areas considerable numbers of pigment cells were present in the meshwork and they occasionally extended into the collector channels. Several completely normal canal outlets and intrascleral channels were seen.

Wet flat preparations of the scleral and uveal meshwork were made from the right eye, and they confirmed that the increased cellularity was mainly due to the entrapment of pigment cells. This was not greater than is seen in some normal eyes and there was no evidence of any kind of obstruction in the meshwork. The uveal fibres, however, differed markedly from the normal in that they gave an intense blue reaction with the iron method of Rinehart-Abul-Haj, suggesting that the fibres were abnormally swollen for I have found in the cornea that swelling of the mucoid-collagen complex leads to an increase in iron affinity and a diminution in collagen staining (Ashton, 1958). The swelling could be readily seen in individual fibres which showed gross thickening of the outer hyaline layer. In some areas the fibres of the hyaline layer appeared to have broken and retracted away from the central collagenous core. All these abnormal appearances, however, could be due to post-mortem degeneration and there is nothing to suggest that they are specific for glaucoma. I would, therefore, sum up our findings as follows:

(1) No microscopical methods for the investigation of angle structures are available to-day which are sufficiently free from artifact to provide completely reliable evidence in the solution of the glaucoma problem.

(2) With this reservation in mind and assuming for the moment a single ætiology in simple glaucoma, the following conclusions may be drawn from the examination of this early case:

(*a*) Simple glaucoma in its initial stages does not appear to be due to any abnormality of the canal outlets themselves.

(*b*) Nor does simple glaucoma appear to be due to any sclerotic or proliferative process within the trabeculæ. Trabecular sclerosis is almost certainly a secondary development since it can occur in late cases of glaucoma from any cause.

(*c*) It is still entirely uncertain from this and other pathological examinations whether simple glaucoma may arise primarily through obstruction of the intrascleral channels.

(*d*) It is possible, though completely unproven, that this disease may begin with microscopical degenerative changes in the trabecular fibres, leading to collapse of the meshwork with diminution in its porosity. A vicious circle might then be set in train through the resulting hypertension inducing secondary changes of trabecular sclerosis, obliteration of the canal (first by the collapsed meshwork and then by adhesions), and finally obliteration of the scleral channels themselves.

We still need much more evidence of the changes to be found in the whole of the outflow pathway in early cases of simple glaucoma in which the clinical picture is fully documented. Little further information is likely to be gleaned from studies confined to the trabeculæ alone or to the outflow channels alone, or from

observations on material from advanced cases. Until these complete data are available any final conclusions on the significance of structural changes would be premature.

REFERENCES

ASCHER, K. W., and SPURGEON, W. M. (1949) *Amer. J. Ophthal.*, **32,** 239.

ASHTON, N. (1955) *In:* Anatomy and Pathology of Drainage Channels in Glaucoma. Edited by W. S. Duke-Elder. Springfield, Ill.; p. 13.

—— (1958) *In:* The Transparency of the Cornea. A Symposium. C.I.O.M.S. (In press.)

——, BRINI, A., and SMITH, R. (1956) *Brit. J. Ophthal.*, **40,** 257.

BÁRÁNY, E. (1953) *Acta Soc. med. upsal.*, **59,** 260.

——, BERGGREN, L., and VRABEC, F. (1957) *Brit. J. Ophthal.*, **41,** 25.

——, and WOODIN, A. M. (1955) *Acta physiol. scand.*, **33,** 257.

BENDITT, E. P., and FRENCH, J. E. (1953) *J. Histochem. Cytochem.*, **1,** 315.

BERGGREN, L., and VRABEC, F. (1957) *Amer. J. Ophthal.*, **44,** 200.

BRINI, A. (1956) *Bull. Soc. Ophtal. Fr.*, p. 256.

—— (1957) *Ann. Oculist., Paris*, **190,** 755.

DVORAK-THEOBALD, G., and KIRK, H. Q. (1956) *Amer. J. Ophthal.*, **41,** 11.

FRANÇOIS, J., NEETENS, A., and COLLETTE, J. M. (1956) *Amer. J. Ophthal.*, **41,** 651.

——, RABAEY, M., and NEETENS, A. (1956) *Arch. Ophthal., Chicago*, **55,** 193.

LANGLEY, R. K., and MCCULLOCH, C. (1958) *Amer. J. Ophthal.*, **45,** 65.

PEDLER, C. (1956) *Trans. ophthal. Soc. U.K.*, **76,** 51.

PETER, P. A., LYDA, W., and KRISHNA, N. (1957) *Amer. J. Ophthal.*, **44,** 198.

TENG, C. C., PATON, R. T., and KATZIN, H. M. (1955) *Amer. J. Ophthal.*, **40,** 619.

——, KATZIN, H. M., and CHI, H. H. (1957) *Amer. J. Ophthal.*, **43,** 193.

VRABEC, F. (1957*a*) *Brit. J. Ophthal.*, **41,** 20.

—— (1957*b*) *Amer. J. Ophthal.*, **44,** 7.

ZIMMERMAN, L. E. (1957) *Amer. J. Ophthal.*, **44,** 1.

Dr. John Speakman (Institute of Ophthalmology, London, England, and Department of Ophthalmology, University of Toronto, Canada):

The Development and Structure of the Normal Trabecular Meshwork

In this study an attempt has been made to elucidate further some of the problems related to the normal anatomy of the meshwork, employing for this purpose *teased* preparations of premature baby eyes from six months to term and adult eyes removed because of suspected intra-ocular tumours. The baby eyes studied were fixed in formalin shortly after death, and the adult eyes were fixed in formalin following enucleation. It will be shown later that this is not adequate to prevent post-mortem change in certain of the corneal and trabecular cells.

I shall discuss three aspects of the normal anatomy of the meshwork:

(1) Development.

(2) The anatomy of the drainage channels with particular reference to the region adjacent to Schlemm's canal.

(3) Vacuolation in the cells of the meshwork.

The Development of Openings in the Trabecular Meshwork

Paraffin sections show that the *fœtal* meshwork is highly cellular and the collagen fibres are difficult to identify. In thin flat preparations, however, it is possible to recognize the beginning of the adult uveal and corneo-scleral meshwork. Some of the openings in the *uveal meshwork* are well differentiated but elsewhere a membrane of cytoplasm extends like a diaphragm between the fibres.

Intermediate stages can be recognized in which one or more circular perforations are present in the cytoplasmic membranes. In the adult eye the openings in the uveal meshwork are very much larger and only occasional cytoplasmic membranes are present between the fibres.

The fœtal *corneo-scleral* meshwork by six months has differentiated into thin sheets of cells in which a number of primary well-defined circular and spiral openings can be recognized. Between the syncytium of cells forming the thin lamellæ, fine collagen fibres are formed which become heavy collagen beams in the adult eye.

It can also be deduced from a comparison with the adult eye that many secondary openings form during growth as a result of perforations in the cytoplasmic membranes forming the fœtal lamellæ. In the adult meshwork one can also see fine strands of cytoplasm crossing the clefts and spaces between the lamellæ and it seems probable that these too form as a result of attenuation of the cytoplasm during growth of the eye.

One can conclude, therefore, from a comparison of the structures in the fœtal and adult eye that a remarkable degree of growth and differentiation occurs in the trabecular meshwork which accounts for the altered configuration of the filtration angle with age. A special process

of cleavage has been postulated by Allen *et al.* (1955) to explain the development of angle structures and they feel that buphthalmos results from a cleavage failure. We found no evidence to support this view. Our findings suggest on the contrary that buphthalmos is probably due to an incomplete differentiation of the openings in the meshwork.

Anatomy of the Drainage Channels

The openings in the uveal meshwork are large and aqueous can easily pass through this layer to the underlying corneo-scleral meshwork to which the uveal fibres are intimately connected. Anteriorly the fibres are embedded in a hyaline-like substance which forms Descemet's membrane, and posteriorly there are numerous attachments to the connective tissue of the iris and muscle fibres of the ciliary body. Contractions of the ciliary muscle may influence the porosity of the meshwork as a result of these connexions.

The corneo-scleral meshwork consists of a complex network of interlacing collagen beams in which there are numerous clefts and openings. In assessing its true porosity, however, one must consider the cellular elements which adhere to the fibres and stretch across the inter-lamellar spaces. Near the canal of Schlemm the collagen fibres run nearly parallel to its lumen forming a series of troughs and crests, and the openings in the lamellæ become long slits.

The spaces between the lamellæ are more accurately described in this region as a series of intercommunicating channels or tunnels. They are outlined by the parallel fibres forming their walls, are about 10 μ in width, and can be traced for distances of 30 to 50 μ. Occasionally one can see pleomorphic cells adhering to the walls and some of these may be macrophages or melanophores which have wandered through the meshwork from the anterior chamber.

An examination of flat preparations of the trabecular wall of the canal shows many round and ovoid openings, previously described by Ashton *et al.* (1956), through which aqueous can drain directly into the lumen of the canal from the channels in its wall. The openings vary in size from 3×5 μ to 8×12 μ. It is not possible to determine their total number accurately but in one oil immersion field seven openings were counted.

In addition to the openings on the inner wall several endothelial lined grooves were noted 5 to 20 μ in width and up to 40 μ in length. Impressions of these can also be seen in Neoprene casts of the canal wall. Occasionally the narrow grooves open directly into the meshwork but the larger ones appear to connect with the meshwork only through smaller openings which are approximately 10 μ in diameter. From these observations it seems clear that many of the endothelial lined defects seen in paraffin sections of the canal wall, which are referred to in the literature as Sonderman's canals, are not true openings into the meshwork, but are due to the grooves on the trabecular wall.

The unequivocal demonstration of openings on the wall of Schlemm's canal should bring an end to the controversy and disagreement in the literature regarding the nature of the filtration channels in this region.

Vacuolation in the Endothelial Cells of the Trabecular Meshwork and Cornea

A remarkable degree of vacuolation is present in the endothelial cells lining the trabecular wall of Schlemm's canal. The vacuoles are frequently found at each end of the fusiform nuclei and may be 5 μ in diameter. A very much finer vacuolation may be seen in the cytoplasm surrounding the trabecular fibres and in some of the clefts the vacuoles assume similar proportions to those seen on the wall of the canal. In a section it may be very difficult to differentiate the larger vacuoles from strands of cytoplasm crossing the gaps between the fibres. It is important to appreciate that these findings occur in an otherwise normal meshwork and they are not a specific pathological finding peculiar to glaucomatous eyes.

A similar gross vacuolation was noted in the endothelial cells of the cornea, although because the cells are packed closely together, the vacuoles are more numerous. A study of fresh unfixed rabbit corneæ, placed in warm Tyrode's solution, was made with the phase microscope. It was possible to see the vacuoles gradually fill and later burst the endothelial cells. This phenomenon, which occurs very rapidly, appears to be related to the role of endothelium in maintaining corneal deturgescence. The similar appearance of the trabecular endothelial cells suggests that they may function in the same way, particularly in the region of the canal wall.

The significance of these findings in relation to the pathogenesis of open angle glaucoma cannot be assessed at present. Could it be that in some cases the process begins as a functional disorder of these cells?

SUMMARY

Our study of the normal anatomy of the trabecular meshwork has shown:

(1) As development of the eye progresses there is a marked increase in the *size* and *number* of the openings in the lamellæ which is associated with an increased deposition of collagen.

(2) Near the canal of Schlemm the aqueous travels through the meshwork in a series of thin-walled intercommunicating channels which enter directly into the lumen of the canal by means of numerous ovoid openings approximately 10 μ in diameter. The total number of these present in a single eye could not be determined accurately but in one oil immersion field it was possible to identify seven.

(3) The cells lining the trabecular wall of Schlemm's canal show a remarkable degree of vacuolation very similar in appearance to vacuolation in the corneal endothelium, which occurs as a result of the post-mortem imbibition of fluid. This may indicate a functional similarity between these cells, and suggests that *in vivo* they might have an important role in preventing swelling of the innermost trabecular fibres.

REFERENCES

ALLEN, L., BURIAN, H. M., and BRALEY, A. E. (1955) *Arch. Ophthal., Chicago*, **53**, 783.

ASHTON, N., BRINI, A., and SMITH, R. (1956) *Brit. J. Ophthal.*, **40**, 257.

BOOKS RECENTLY PRESENTED AND PLACED IN THE SOCIETY'S LIBRARY

Ribeiro do Valle (J.). Farmacologia teórico-prática. pp. 307. São Paulo: Laboratorios de Farmacologia e Bioquimíca da Escola Paulista de Medicina. 1955.

Salerno. The School of Salernum. Regimen sanitatis Salerni. English version by Sir John Harington. pp. 92. Salerno. 1953.

Samuels (J.). Endogenous endocrinotherapy (Samuels therapy) including the causal treatment of cancer compendium. 9th ed. pp. 554. Amsterdam: Cycloscoop. 1958.

Solomon (H. C.), and **Solomon (M. H.).** Syphilis of the innocent. pp. 239. Washington: Interdepartmental Social Hygiene Board. 1922.

Spence (Sir James C.). The care of children in hospitals. (The Charles West Lecture, 1946.) pp. 16. Harpenden. 1946.

Symonds (Sir Charles P.). The circle of Willis. The Harveian Oration of 1954. pp. 16. London. 1955.

Trumble (H. C.). The collected papers of Hugh Trumble. pp. 302. Melbourne: University Press. 84s. 1957.

United States. National Conference on Research and Education in Rheumatic Diseases. Research and education in rheumatic disease. Trans. of 1st National Conference, 1953; Trans. of 2nd National Conference, 1956. New York: Arthritis and Rheumatism Foundation. 1954, 1957.

Verboom (C. H.). Zieke zuigelingen. 3rd ed. pp. 302. Assen: Van Gorcum. 1955.

Wallgren (A. J.). In honour of Arvid Wallgren on his 65th birthday, October 5, 1954. pp. 635. Stockholm: Almqvist and Wiksell. 1954.

White (C. S.), et al. Aviation medicine: selected reviews. pp. 305. London: Pergamon Press. 70s. 1958.

Whittet (T. D.). Experiments on the occurrence of pyrogens in water and their removal and on their pharmacology and fate in the body. pp. 207. London University, PhD. Thesis. 1958.

Winnicott (D. W.). Collected papers: through pædiatrics to psycho-analysis. pp. 350. London: Tavistock Publications. 1958.

Wolf (H.-J.). Die Krankheit Friedrichs III. pp. 160. Berlin: Berliner Medizinische Verlag. 1958.

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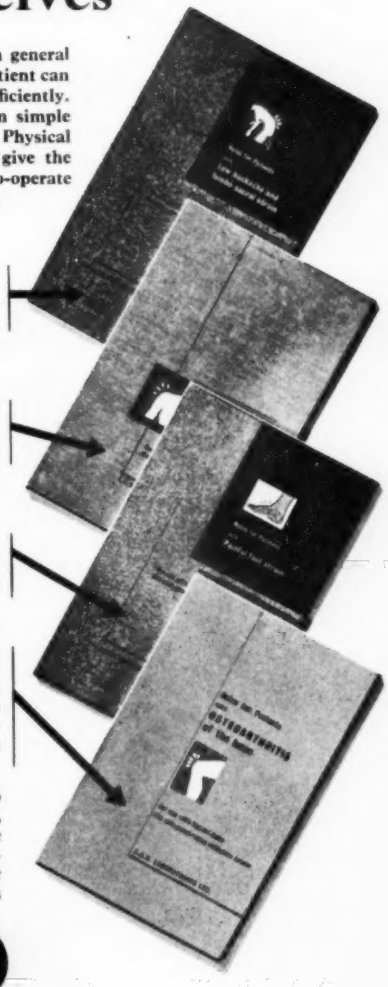

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Section of Pædiatrics

President—CHARLES PINCKNEY, F.R.C.P.

Meeting
October 24, 1958

DISCUSSION ON THE SIGNIFICANCE OF CARDIAC MURMURS IN THE FIRST FEW DAYS OF LIFE

Dr. Aubrey Leatham (London):

Introduction

As I possess no special knowledge of cardiac murmurs at this stage of infancy and since investigations by others are few and are difficult to perform, I shall briefly review the possible mechanism of such murmurs.

Most murmurs are related to increased velocity of flow and fall into three main groups:

(1) High rates of flow through normal or abnormal valves.

(2) Forward flow through a constricted or irregular valve or into a dilated vessel.

(3) Backward flow through a regurgitant valve, septal defect or patent ductus arteriosus.

Large pressure differences and small orifices produce the highest blood velocity and loudest murmur (e.g. small ventricular septal defect or severe pulmonary stenosis), while small pressure differences across big defects may produce large flows without a murmur (e.g. atrial septal defect). Small flows across big defects are even less likely to cause a murmur. This explains why forward flow or right-to-left shunt through a patent ductus arteriosus, or a ventricular septal defect, is silent, for, to be compatible with life, the shunt is necessarily small and the defect in these cases seems always to be large.

At birth with the onset of breathing the resistance to the flow of blood through the pulmonary circulation falls tremendously but is still high and about the same as the systemic resistance. Thus the pressures in the aorta and pulmonary artery, and in the left and right ventricles are about the same, and any flow through a defect connecting them will be small. Dawes has shown in lambs (Dawes *et al.*, 1955), and Adams and Lind (1957) in man, that a small left-to-right shunt from aorta to pulmonary artery takes place during the first few hours or days of life, though the difference in pressure is so slight that the shunt can be reversed by crying (Eldridge *et al.*, 1954). At this stage no murmurs can be heard because the shunt is small and the defect large and, similarly, no murmur would be expected from a ventricular septal defect of any appreciable size. When the ductus is closing, producing increased velocity of blood flow, brief murmurs have been heard and recorded by Dawes *et al.* (1955) and by Burnard (1958).

With large ducts and ventricular septal defects the pulmonary resistance appears to remain very high, at systemic levels, from birth (Wood, 1958*a*), and prevents fatal flooding of the lungs; no appreciable shunt murmur will ever appear in these cases. With small or moderate sized defects, the pulmonary resistance, and therefore pressure, can fall without being fatal, and the increased velocity of the left-to-right shunt produces the characteristic murmur.

The pressures in the left and right atria may not share in this changing relationship, for the left-to-right shunt from the ductus has increased the return of blood selectively to the left atrium and the higher pressure in this chamber closes the valve of the foramen ovale if the interatrial septum is intact. If there is a defect in the interatrial septum, the higher pressure in the left atrium should cause a left-to-right shunt and the usual signs of atrial septal defect. These signs are difficult to detect and may be transient, for the pressure gradient between left and right atria probably ceases when the duct closes, since the walls of the left and right ventricle are equally thick and offer an equal resistance to ventricular filling (Edwards, 1957; Wood, 1958*b*).

Thus shunts may be only potential, and difficult to diagnose, in neonatal life. Congenital valvular disease, however, is expected to produce the adult type of murmur.

Phonocardiography is the graphic registration of heart sounds and murmurs and should prove of great value in the elucidation of these problems in the neonatal period. Recordings should be made at high paper speeds so that tachycardia will not cause overcrowding of sounds and murmurs. In the first place, filters should be used to cut low frequencies so that the graph resembles the findings of auscultation. Not only will the clinical correlation be valuable, but these records will probably give the best relation to the hæmodynamics, as they have in adults. A clinical classification of systolic murmurs based on phonocardiography has been suggested (Leatham, 1958):

(1) Midsystolic ejection murmurs caused by

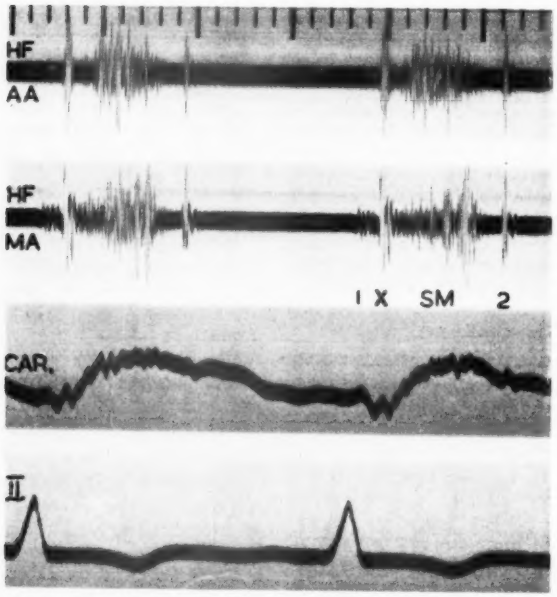

FIG. 1.—Midsystolic ejection murmur in a patient with aortic stenosis. The murmur ceases before aortic closure.

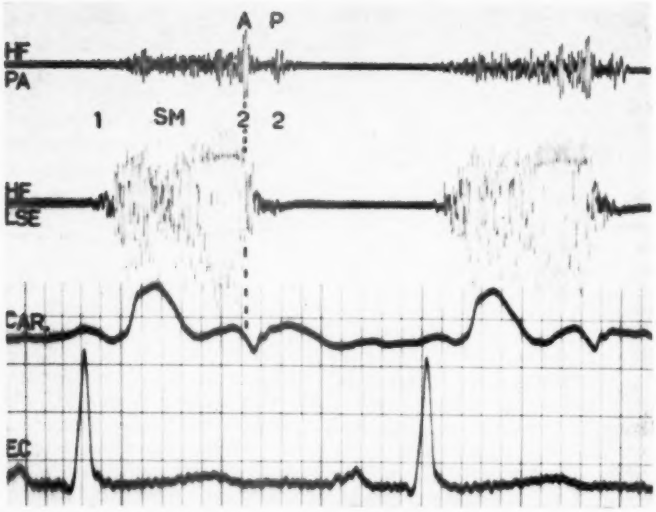

FIG. 2.—Pansystolic regurgitant murmur in a patient with a ventricular septal defect, low pulmonary resistance and left-to-right shunt. The murmur reaches and embraces aortic closure.

the forward flow of blood through the aortic or pulmonary valves.

(2) Pansystolic regurgitant murmurs due to back-flow of blood from ventricles to atria through incompetent valves or to left-to-right shunts through a ventricular septal defect or patent ductus arteriosus when the right-sided pressures are low.

Ejection murmurs fall off in intensity with diminishing flow towards the end of systole and cease before valve closure (Fig. 1). With "regurgitation" from the high pressure left ventricle to the low pressure left atrium, or right ventricle, or from aorta to a low pressure pulmonary artery, both flow and murmur continue up to and beyond aortic or pulmonary closure (Fig. 2) for, at this time, there is still a difference in pressure between the donating and receiving chambers or vessels. These principles may be applied to the murmurs encountered in patients with patent ductus arteriosus and ventricular septal defect.

Patent ductus arteriosus is associated with three types of murmur, depending on the hæmodynamics, and only two are due to flow through the duct. The continuous murmur found in adults is due to a continuous shunt of blood from the high pressure aorta to a low pressure pulmonary artery. In infants the murmur of patent ductus arteriosus is described as systolic alone, even when the shunt is left-to-right. This is presumably due to the relatively high pulmonary resistance of the infant and in the few whom we have investigated the difference in pressure between aorta and pulmonary artery has been confined to systole, thus accounting for the systolic flow and murmur. The murmur is pansystolic and thus easily distinguished from aortic or pulmonary ejection murmurs. In patent ductus with high pulmonary vascular resistance the small flow through the large duct is silent, though pulmonary ejection and regurgitant murmurs are common when the pulmonary artery is greatly dilated.

Similarly in ventricular septal defect the murmur is almost invariably pansystolic when the pressure in the right ventricle is low, and absent when the pressures in the two ventricles are about the same. In the latter group with high pulmonary resistance and a ventricular septal defect, as with a ductus, the dilated pulmonary artery may produce an ejection and a regurgitant murmur.

REFERENCES

ADAMS, F. H., and LIND, J. (1957) *Pediatrics, Springfield*, **19**, 431.
BURNARD, E. D. (1958) *Brit. med. J.*, i, 806.
DAWES, G. S., MOTT, J. C., and WIDDICOMBE, J. G. (1955) *J. Physiol.*, **128**, 344.
EDWARDS, J. E. (1957) *Circulation*, **15**, 164.
ELDRIDGE, F. L., HULTGREN, H. N., and WIGMORE, M. E. (1954) *Science*, **119**, 731.
LEATHAM, A. (1958) *Lancet*, ii, 703, 757.
WOOD, P. (1958*a*) *Brit. med. J.*, ii, 701.
—— (1958*b*) *Brit. Heart. J.*, **20**, 557.

Dr. Geoffrey Dawes (Oxford) discussed the causation of murmurs and the ductus murmur in particular, basing his remarks on work already published in physiological journals (Born *et al.*, 1954; Dawes *et al.*, 1955; Amoroso *et al.*, 1958). He emphasized that murmurs were due to turbulent flow, and that such murmurs were always found over the ductus arteriosus in newborn lambs, calves and foals. In contradistinction to Dr. Leatham, he pointed out that the left-to-right flow through the patent ductus after birth was very large, amounting to as much as half the cardiac output, in both animals and babies (Adams and Lind, 1957; James and Rowe, 1957; Rowe and James, 1957) and that there is a large fall in pulmonary arterial pressure after birth.

REFERENCES

ADAMS, F. H., and LIND, J. (1957) *Pediatrics, Springfield*, **19**, 431.
AMOROSO, E. C., DAWES, G. S., and MOTT, J. C. (1958) *Brit. Heart J.*, **20**, 92.
BORN, G. V. R., DAWES, G. S., MOTT, J. C., and WIDDICOMBE, J. G. (1954) *Cold Spr. Harb. Symp. quant. Biol.*, **19**, 102.
DAWES, G. S., MOTT, J. C., and WIDDICOMBE, J. G. (1955) *J. Physiol.*, **128**, 344, 361.
JAMES, L. S., and ROWE, R. D. (1957) *J. Pediat.*, **51**, 5.
ROWE, R. D., and JAMES, L. S. (1957) *J. Pediat.*, **51**, 1.

Dr. E. D. Burnard (London):

A Murmur that May Arise from the Ductus Arteriosus in the Human Baby

A murmur which possessed certain characteristic properties was heard in 37% of 100 apparently healthy full-term babies and in 57% of 96 premature babies. It had a rough, high-pitched quality and occurred in the latter part of systole. It sometimes continued into early diastole, through the second sound, which was always loud when the murmur was present. The murmur was seldom loud, and usually was best heard at the 3rd or 4th left costal cartilage; sometimes it radiated more widely. There was always an interval of time from birth to the first detection of the murmur, in most instances between fifteen minutes and two hours.

Phonocardiograms confirmed that the murmur occurred late in systole and sometimes continued through the second sound, and that its pitch was fairly high. The murmur became louder during inspiration and disappeared with expiratory straining, a form of fluctuation which might account for some of the difficulty in its detection. By analogy with the findings in other newborn mammals, and because of the relatively high

pitch, the downward radiation when loud, and the continuation beyond the second sound, the murmur has been attributed to flow through the ductus arteriosus from aorta to pulmonary artery.

The murmur was not heard after the age of 10 hours in mature, apparently healthy babies. In premature babies it lasted longer, and was present in 10% at the age of 48 hours.

The murmur was related to clinical events. The apparently healthy mature babies in whom it was heard had in fact suffered birth asphyxia in most instances: it was found only very rarely after normal birth in full-term babies. In premature babies the murmur occurred whether there had been asphyxia at birth or not: in them there was a clear connexion with dyspnœa, and the murmur was not heard unless respiratory distress was present. In some prematures the murmur disappeared and then returned if their condition deteriorated. Mature babies who became ill with respiratory embarrassment after birth asphyxia were similar to premature babies in the more ready detection and longer duration of the murmur. There seemed therefore to be some connexion between birth asphyxia or prematurity on the one hand, and the murmur and difficult breathing on the other.

The murmur was related to rectal temperature. The temperatures of babies in whom the murmur was present after birth asphyxia were significantly higher than when the murmur was absent. Conversely, when babies who had not been asphyxiated were kept warm the murmur developed in a significantly higher proportion (30%) than in babies who were not kept warm (7%).

There is good evidence that the ductus arteriosus remains open for twenty-four hours or more after birth in the human baby, as in the lamb. The fact that the murmur has only rarely been heard after normal birth suggests that in the situations where it was detected, which have been described above, there was a departure from the normal conditions governing flow across the ductus.

Its occurrence at higher temperatures suggests that when the murmur is present flow across the ductus is greater than normal. The principal value of the murmur at present, however, lies in the association that can be recognized with abnormal stress, namely asphyxia at birth or respiratory embarrassment.

Dr. R. E. Bonham-Carter (London):

Prognosis

Estimates of the incidence of congenital malformations of the heart are rising with better observation and methods of investigation. Keith *et al.* (1958) says 5 per 1,000 live births; Carlgren (1958) says 6 per 1,000 live births. It may well be even higher.

The recorded incidence of murmurs heard in neonates depends upon the diligence and acuity of the observer more than anything else. But the definition of the neonatal period also contributes. The excellent paper on this subject by Richards *et al.* (1955) puts it as high as 17 per 1,000 live births.

The recorded incidence at University College Hospital has varied widely with the keenness of hearing and otherwise of the observers, but averages around 10–12 per 1,000 live births. We became interested in these noises ten years ago and have been following them since. All have been heard by two people, the majority by three or more.

For the purposes of this discussion I propose to deal with those heard in the first 14 days, though we have 11 more heard in the second fortnight of life.

The teaching has been that most of these murmurs are not significant. Our experience is that this is not so (Table I).

TABLE I

Total live births 9 years to 1957 ..	11,855
Total murmurs heard 1–14 days ..	99
Total followed	88
Persistent	49
Significant (investigated)	29
Dead	15

The next group (Table II) are particularly interesting and would not have come to light but for the follow up. They are recurring murmurs.

TABLE II

Murmurs disappearing and recurring	17
Significant (investigated)	8
Persistent (not investigated) ..	7
Disappeared again	2

The importance of this study is only that murmurs heard in the first few weeks of life are in the majority significant. Those that vanish apparently for ever do so usually within the first week of life. Some murmurs recur and are significant. So all murmurs heard at this time should be followed.

My thanks are due to all the pædiatric registrars and housemen we have had at U.C.H. during this period and particularly to Dr. Jean Smellie and Dr. Philip Benson who have organized the follow up.

REFERENCES

KEITH, J. D., ROWE, R. D., and VLAD, P. (1958) Heart Disease in Infancy and Childhood. New York.

CARLGREN, L. E. (1958) Unpublished data.

RICHARDS, M. R., MERRITT, K. K., SAMUELS, M. H., and LANGMAN, A. G. (1955) *Pediatrics, Springfield*, **15**, 169.

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BOOK REVIEWS

Principles of Medicine and Medical Nursing. By J. C. Houston, M.D., F.R.C.P., and Marion Stockdale, S.R.N., S.C.M., R.S.C.N. (Pp. ix+198; illustrated. 15s.) London: English Universities Press Ltd. 1958.

The aim of the authors to provide at a moderate price "a sound and reasonable introduction to present-day medicine" has been well fulfilled.

The subject matter is clear and concise and is illustrated by simple, clear diagrams.

Obviously in a book of this size it is impossible to mention all the diseases a nurse is likely to meet during the medical part of her training. It is, however, surprising to find no mention of acne vulgaris in the section on skin diseases, or of threadworm infestation in the chapter on diseases due to worms.

Details of nursing care vary in the different training schools, but the use of glycerine of borax for application to a dry, coated tongue is now considered by many physicians to encourage the growth of monilia. Furthermore, the instruction on page 138: "a spoon or other blunt object should be forced between the teeth of a patient" in an epileptiform convulsion has been condemned by neurologists.

As the table of physiological normals at the end of the book includes the normal composition of C.S.F., it would be more satisfying to the intelligent student if the "fairly typical changes" quoted on page 118 in poliomyelitis were more specifically mentioned as "an increase of protein".

These are, however, minor criticisms and the authors are to be congratulated on producing an excellent, concise textbook.

Amphetamine Psychosis. By P. H. Connell, M.D., D.P.M. Maudsley Monographs No. 5. (Pp. 133; illustrated. 21s.) London, Chapman & Hall, Ltd. 1958.

This monograph describes some 42 cases of such addiction or intoxication seen at the Maudsley or Bethlem Hospitals, mostly between 1953 and 1956, and analyses 36 other cases from the literature. Forty-two pages are devoted to the description of a valuable test for demonstrating the drug in the urine. Many patients consume the contents of inhalers.

The book criticizes the Ministry of Health's Annual Report 1954, which states "These drugs have the advantage of being relatively non-toxic; addiction to them is rare and there are no serious ill-effects; they may therefore be given to out-patients without undue risk." The author contends, however, that a psychosis may result which is indistinguishable from schizophrenia and there may be no family history or typical pre-psychotic personality. The drug is in fact a true hallucinogen. Addiction is more frequent than is generally supposed. There can be serious toxic effects in both the mental and physical spheres. Addiction is difficult to cure. The drug should, therefore, not be prescribed except as part of a definite limited course of treatment.

The situation, however, is likely to improve now that the drug in pill form comes under Schedule IV, but it is regrettable that at least one of the biggest manufacturers still sells 250 mg. inhalers.

Metabolic Disturbance in Clinical Medicine. Ed.: G. A. Smart, B.Sc., M.D., F.R.C.P. (Pp. vii+358; illustrated. 45s.) London: J. & A. Churchill, Ltd. 1958.

New light has recently been thrown on many diseases as a result of the detailed metabolic studies made possible by improved analytical methods, as well as by the application of isotopes, flame photometry and chromatography. Since much of this work has been written up in review articles and original papers in numerous journals, Professor Smart's book fills an important gap in presenting an account of the metabolic disturbances which may be encountered in clinical medicine. As is to be expected from a book written by a number of authors, the treatment is somewhat uneven, and there is some overlap in the subject matter with that of "Biochemical Disorders in Human Disease" by Thompson and King. Emphasis tends to be slightly in favour of the clinical aspects in the book at present under review. Chapters which are especially good are by Black on water and electrolytes and on the metabolic aspects of renal disease, and the account by Wilson, Moore and Jepson of the work of the Boston School on the metabolic disturbances following injury. Chapters on oxygen therapy, lung function and acid base balance, and on disturbances of metabolism affecting the central nervous system are also very useful. The book is well documented by an excellent series of references which are sufficiently up to date to extend to 1957.

Florence Nightingale and the Doctors. By Sir Zachary Cope. (Pp. ix+164; illustrated. 21s.) London: Museum Press Ltd. 1958.

This is a welcome addition to the literature dealing with the story of one of the more remark-

able and interesting personalities of the Victorian era. In his preface the author expresses the hope that his account, which reproduces extracts from letters not hitherto made public, may throw a clearer light upon Florence Nightingale's curious and highly complex nature. This it certainly does. She seems to have found the majority of doctors easier to get on with than most of her contemporaries: e.g. "I can always talk better to a medical man than to anyone else. They have not that detestable nationality which makes it so difficult to talk with an Englishman."

The selection of extracts from Miss Nightingale's correspondence with distinguished members of the medical profession is well chosen: suitably arranged as they are, in company with some necessary historical details of her career, they make very interesting reading.

The more polemical aspects of her relations with the medical authorities during the Crimean war are treated with that judicial fairness which is so characteristic of Sir Zachary Cope:

"Miss Nightingale must have been able and very willing to supply a lot of useful information to the (Sanitary) Commissioners who found it difficult to criticize the sanitary conditions of the hospitals without implicating the chief medical officer, Dr. (afterwards Sir John) Hall, and the Director-General of the Army Medical Service, Sir Andrew Smith. There is no doubt that Miss Nightingale regarded Dr. Hall as typical of the system which had broken down under the strain of war, and Dr. Hall on his part regarded Miss Nightingale as an interloper who was in some respects undermining his authority. There was truth in both of these points of view."

Of special interest is the account of the correspondence with Sir Henry Acland and others about the training of nurses and the granting of certificates of proficiency, a proposal to which, curiously enough, Florence was at the time strongly opposed.

The illustrations are good, and the general format of the book is pleasing. We congratulate both the author and the publishers.

Non-Venereal Syphilis. A Sociological and Medical Study of Bejel. By Ellis Herndon Hudson, M.D., D.T.M. & H.(Lond.), F.A.C.P. (Pp. vii + 204; illustrated. 30s.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

Dr. Hudson, out of a not inconsiderable experience, has written in time past a great deal of interest about treponemata and the diseases they may cause in man. In this book he concentrates on bejel, but inevitably there are sections on syphilis, yaws and pinta and the interrelationship between these four diseases which, Dr. Hudson believes, are caused by the same historic organism, variations in their manifestations being due to changes in the environment of the hosts. Dr. Hudson discusses the Columbian view of syphilis fully and interestingly, and suggests very credibly that it is nonsense. He goes on to write about bejel, basing the discussion on his own experiences at his clinic in Deir-ez-Zor, in the Euphrates valley. Its epidemiology, sociology, clinical science, serology and histology are clearly and interestingly described. Since his researches into the subject were in the pre-penicillin era, there is less said about treatment than about other aspects of the disease. The black and white photographs are quite outstandingly good and intriguing. An esoteric subject this may be, but travel books are always satisfactory things to read, and only the dull doctor will get nothing out of this one.

The Forequarter Amputation. By H. F. Moseley, M.A., D.M., M.Ch.(Oxon), F.R.C.S.(Eng. and Canada), F.A.C.S. Illustrated by Helen T. MacArthur, B.A. (Pp. viii + 79; illustrated. 42s.) Edinburgh and London: E. & S. Livingstone Ltd. 1957.

The industry of the author is inexhaustible, for he tells us that this is the sixth publication in which he has had the valuable aid of Miss Helen MacArthur, the gifted medical illustrator at the Royal Victoria Hospital, Montreal. The Assistant Professor of Surgery has first-rate qualifications for writing this book, since his own particular contributions to the textbook of surgery which he edits deal with fractures and other disorders of the extremities; moreover, the Hunterian Lecture which he delivered at the Royal College of Surgeons of England concerned itself with an orthopædic problem.

To the reviewer the illustrations depicting the various steps of the Littlewood or posterior approach to the amputation seem particularly helpful; the author correctly points out that this is the more rapid method of amputation. Nevertheless, the amputation, whether performed by the Berger or the Littlewood technique, is a simple operation, and without any desire to be a captious critic the Horatian "tag" keeps ringing in one's ears: "*Parturiunt montes, nascetur ridiculus mus.*"

The author has rendered a service to those with a historical penchant by collecting and arranging in chronological order the traumatic forequarter amputations recorded in the literature. The reviewer has seen two additional cases that have not found their way into the

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printed page: one was that of an officer wounded in the early part of the Third Battle of Ypres in the autumn of 1917; the other was that of a surgeon wounded by enemy air attack on the South coast of England in 1944.

The work is in the best Livingstone tradition, and the author, like many others, has enjoyed the generous help and friendly counsel of Mr. Charles Macmillan.

Sidelights on the History of Medicine. Edited by Sir Zachary Cope. (Pp. x + 246; illustrated. 45s. 35s. to Fellows of the Royal Society of Medicine.) London: Butterworth & Co. (Publishers) Ltd. 1957.

The Jubilee of the Royal Society of Medicine was the occasion for publishing a collection of some 23 lectures upon the history of medicine. The papers are diverse in character and include such topics as Greek medical etiquette (W. H. S. Jones); the medical staff of King Edward III (G. E. Gask); Professional Fees (D'Arcy Power); Humphry Davy's contribution to anæsthesia (F. F. Cartwright); and the History of Ovariotomy (Herbert Spencer). All of the papers are of interest, one of the most intriguing being Guthrie's "The Patient: a neglected factor in the History of Medicine." The papers have been selected and edited by Sir Zachary Cope, who writes a foreword and also contributes a most readable article on surgical lectures one hundred and fifty years ago.

Therapeutic Exercise. Edited by Sidney Licht, M.D. (Pp. xiv + 893; illustrated. $16.) New Haven, Conn.: Elizabeth Licht, Publisher. 1958.

Having already published similar symposia on Electrodiagnosis and Therapeutic Heat, the Physical Medicine Library now completes the trilogy with a comprehensive review on Therapeutic Exercise.

There can be little doubt of the truth of its claim to be "the largest volume ever published on the subject"; 36 authors from both sides of the Atlantic have contributed.

The first 18 chapters are devoted mainly to anatomy, physiology and general principles of rehabilitation. Included are excellent monographs by Nancy Salter and T. F. Hynes on methods of muscle and joint examination and evaluation. C. B. Wynn-Parry describes a series of vicarious movements which can be developed to overcome functional disability resulting from paralysis, and Herman Kabat explains the principles on which his controversial "Proprioceptive facilitation techniques" are based.

The remaining 17 chapters are devoted to detailed accounts of exercise regimes in specific conditions. Finally, the editor contributes a lengthy appendix on miscellaneous techniques which—incredible as it may seem in a book of 893 pages—have not been dealt with by his colleagues.

Whether considered as a reference book or as a series of comprehensive monographs complete with bibliographies, this will undoubtedly be a most useful book not only to specialists in physical medicine but also to physiotherapists, educational gymnasts and all other medical auxiliaries who are interested in rehabilitation techniques.

Inevitably the style and standard of writing are patchy and some of the descriptions of techniques are difficult to follow; however, there can be no doubt that this volume will contribute to the editor's avowed aim that wherever possible vague prescriptions for "rehabilitation" will be replaced by specific instructions for logically planned therapeutic exercises.

The Biologic Basis of Cancer Management. By Freddy Homburger, M.D. (Pp. xvii + 354; illustrated. 75s.) London: Cassell & Co., Ltd. New York: Paul B. Hoeber, Inc. 1958.

Dr. Homburger has discussed in the four parts of his book a great deal of the data which have already been accumulated on: (1) The Etiology of Cancer, (2) The Biological Behaviour of Cancer, (3) The Diagnosis of Cancer, (4) The Treatment and Prevention of Cancer.

Practically every statement made by the author is backed in the text by a reference to some well-known authority on the point under discussion. These references are again listed in an appendix under each chapter and total approximately 1,200 names. To read and to extract all this material has been a gigantic task. It is probable that for the expert in Cancer Research there may not be much that is new in his own particular line, and some of it may be considered controversial, but for the ordinary medical reader it is a fascinating book.

Diffuse Lesions of the Stomach. By Ian J. Wood, M.D.(Melbourne), F.R.C.P., F.R.A.C.P., and Leon I. Taft, M.B., B.S., B.Sc.(Melbourne). (Pp. x + 86; illustrated. 24s.) London: Edward Arnold (Publishers) Ltd. 1958.

The Melbourne school, led by Ian Wood, have pioneered the studies on gastric biopsy, having perfected a new technique which has since had important applications in other fields. This small monograph brings together in 86 pages the details of technique and their observations

on acute gastritis, chronic gastritis, diffuse giant hypertrophic gastritis and pernicious anæmia, together with all important references. It is refreshingly written and authoritative and will remain a little masterpiece for the next generation.

It's Healthy to be Human. By F. R. C. Casson, M.B., B.S., D.P.M. (Pp. 160; 10s. 6d.) London: The British Medical Association. 1958.

In this little book, one of a series published by the British Medical Association, Dr. Casson has outlined, for the benefit of lay people, the nature of instinct, and has described the way in which it works in the human being at the seven main age-periods from infancy to senescence. He has discussed particularly the variability of the three main instincts, hunger, sex and self-assertiveness, and has done it very well. He has fully explained his technical terms—fixation, sublimation and the like—and the book may be confidently recommended to parents who seek to improve their comprehension and control of young children.

The Borderland of Embryology and Pathology. By R. A. Willis, D.Sc., M.D., F.R.C.P. (Pp. ix + 627 + 33; illustrated. 90s.) London: Butterworth & Co. (Publishers) Ltd. 1958.

This magnificent book represents a new departure in both embryology and pathology. In fact, it is designed to bring together the embryologist and the pathologist on common ground in dealing with the subject, not only of congenital malformations, but of those conditions which arise from events in prenatal life.

This is a new approach but obviously one of the greatest importance. The modern embryologist and pathologist together elucidate many conditions, not only malformations but teratomata and inborn errors of metabolism and blood formation.

The book is too large and the scope of the subject too vast to cover in a brief review. The book can be recommended to all interested in the subjects concerned. It is beautifully produced and illustrated and the bibliography is extensive so that it will prove an invaluable work of reference.

Psychiatry and the Public Health. By G. R. Hargreaves. (Pp. 118; 12s. 6d.) London: Oxford University Press. 1958.

This volume contains the Heath Clark Lectures for 1957. The first lecture is a brief summary of the origins and development of psychiatry. Three more are devoted to defining the present position of psychiatry in relation to the community, general practice and the public health service. It is beautifully produced and has an air of academic calm which is deceptive. Professor Hargreaves has taken advantage of his opportunity not only to describe the present state of affairs, but to advocate changes and reforms, particularly in the fourth lecture (which to psychiatrists will perhaps be the most interesting) on psychiatry and medical administration.

Psychiatrists will welcome the publication of these lectures because much is well said that needs saying at this time about, for example, the teaching of psychiatry, the status of child psychiatry, and the co-ordination of outpatient, inpatient and rehabilitation services.

It can be recommended to general physicians, general practitioners and senior students as well as to the Medical Officers of Health for whom it was primarily written.

Clinical Involvements or—The Old Firm. By H. Gardiner-Hill, M.D., F.R.C.P. (Pp. vii + 200; illustrated. 32s. 6d.) London: Butterworth & Co. (Publishers) Ltd. 1958.

The lessons learned from bedside teaching and the methods revealed by a consultant as he approaches a sick patient, are often worth many pages of book reading. Yet, to turn one into the other is almost impossible; to capture the spontaneity and liveliness of a clinical round in the restricted medium of a printed page is unlikely to succeed even when decorated with funny pictures as this book is.

The cases are clearly presented and the maxims they illustrate are sound enough, but they lose a lot of their value because the consultant and the patient are not there. And the pictures: a trap-door opening in the forehead to remind the reader to "keep an open mind"; a broken-down crock of a car to illustrate aplasia of the marrow; they do not add greatly to the material.

Yet despite these imperfections there is a wealth of clinical experience here, an unrestricted range of subjects and the imprint of an enquiring unfettered intelligence. The book makes a stimulating "Companion to Medical Reading" and for ex-members of "The Old Firm" will reawaken old learning and revive pleasant memories.

Theory of Psycho-analytic Technique. By Karl A. Menninger, M.D. Menninger Foundation Series Monograph No. 12. (Pp. xiii + 206; illustrated. 25s.) London: Imago Publishing Company Ltd. 1958.

A brief account is given of the libido theory

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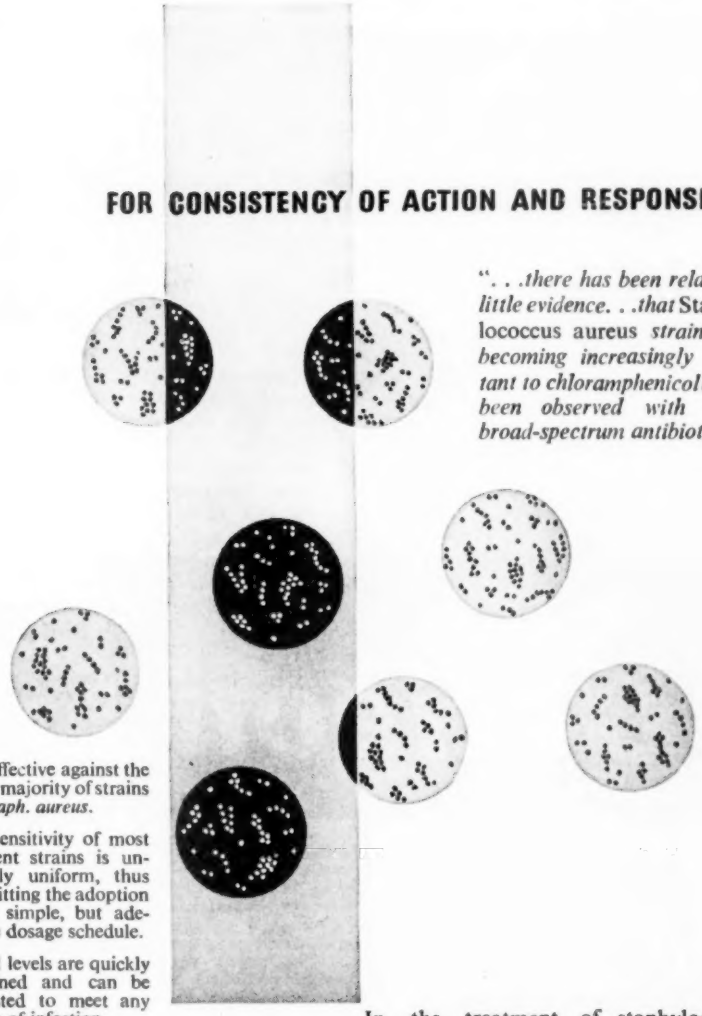

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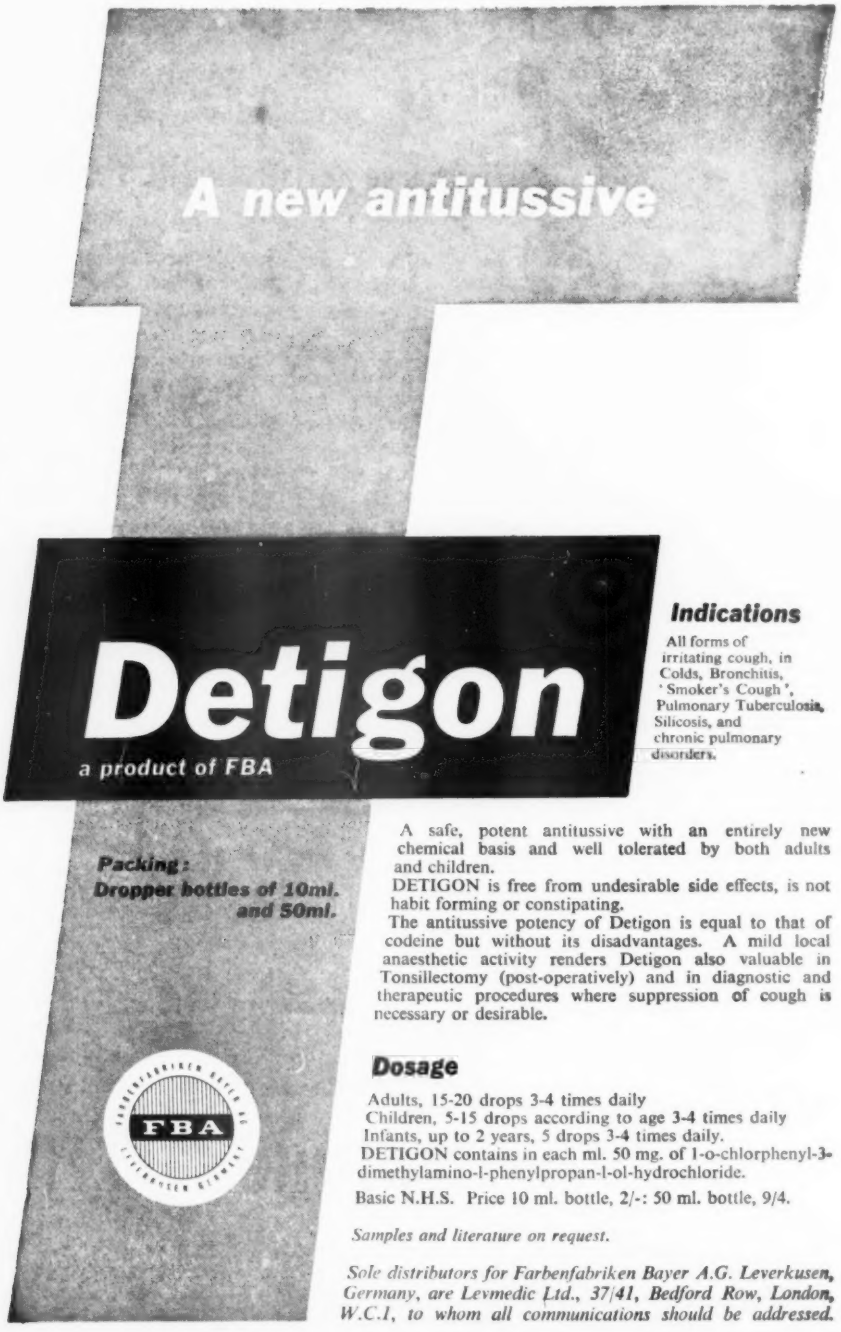

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on which psychoanalysis is based. Dr. Menninger discusses frankly the undercurrent of emotions (transference and countertransference) in the analytic situation. By free association and by recounting his dreams, the patient regresses back to the emotional experiences of childhood. The analyst interprets the patient's irrational attitudes and symptoms in the face of unconscious resistance, until self-understanding has led to better social adjustment.

Although the preceding monograph (No. 11) in this Menninger Clinic series was based on the scientific method, the present one reflects a regressive tendency in American psychiatry. There is much that is offensive to the medical reader. Thus there are more than two dozen references to fees; one patient's failure to improve after two years' treatment was surely not only because someone else was paying for it (p. 35); the words "we know" and "of course" precede the most dubious explanations (p. 118); some analysts are said to feel homosexual urges towards the patient, and so drop the case too soon (p. 176); the analyst is told how to behave if a patient mentions having been seduced by a previous analyst (p. 118); we are told (but is the patient?) that therapeutic success is not of primary importance (p. xi); if we look for facts and figures, we are merely told that "millions have been relieved" by psychoanalysis (p. 178) and "the gains of the treatment are immeasurable" and "extend out into the universe" (p. 179).

If the book is intended for medical men, the writer might have referred more to recent efforts by Franz Alexander and others to evaluate such theories scientifically and to bring what is of value in them into line with other disciplines (*see* Kruse, H. D. (1957) Integrating the Approaches to Mental Disease. London: Cassell & Co. Ltd.), but if it is intended to teach the contents of this book to medical men, it would surely be better to follow Freud's advice (Jones, E. (1953–1957) Sigmund Freud: Life and Work. Vol. III, ch. IX. London: The Hogarth Press) and restrict the practice of psychoanalysis to the laiety.

Chemotherapy and the Central Nervous System. By Henry McIlwain, Ph.D., D.Sc. (Pp. viii + 328; illustrated; 45s.) London: J. & A. Churchill, Ltd. 1957.

The reader would perhaps derive most value if he were to read first, and digest, the author's useful Chapter 12. Herein we find Claude Bernard quoted in apposite fashion: "La fixité du milieu intérieur est la condition de la vie libre." This obiter dictum was modified by Barcroft to "the fixity of the internal environment is in short the condition of mental activity". In other words, constancy of the composition of body-fluids is more important to the functioning of the brain than it is to other bodily activities.

This book is an extremely useful one, for it interprets the data of the pharmacological laboratory for the benefit of the practising doctor. The stupendous advances made in chemotherapy during the past few decades have transformed both the treatment and the prognosis of the sick. It is no easy task for the busy and experienced clinician to keep abreast of these advances, let alone to evaluate them. Professor McIlwain's monograph will materially help. It should be studied over and pondered, particularly by psychiatrists—who, often without preliminary training or aptitude, are to-day presented with a pharmacological armamentarium of unbelievable potency. We suspect that at times these powerful weapons are employed with an insouciance which would cause an ordinary internal physician to tremble. For such practitioners, this book is highly recommended. The chemical terminology is bewildering at times, and when this is combined with the more familiar trade-names, a veritable bilingual state develops. Perhaps the reader's task could be simplified if there were appended a glossary of synonyms. This point is possibly a small one, and should in no way be read as criticism of a very real literary accomplishment.

The Function of the Ureter and Renal Pelvis. Pressure recordings and radiographic studies of the normal and diseased upper urinary tract of man. By Fredrik Kiil, M.D. (Pp. 205 + xii plates; 52s. 6d.) Philadelphia and London: W. B. Saunders Company. 1957.

This book is based upon the author's own experimental studies of the function of the ureter and renal pelvis, but a critical review of most of the relevant literature has been successfully included in the text.

The opening chapters relate to the methods of study and indicate that the experimental conditions have been carefully controlled. In succeeding chapters the methods are applied to an evaluation of the nature of the contraction waves in the ureter and renal pelvis, and to the relationship of contractile activity to urine flow, obstruction or distension, micturition, pregnancy, and various drugs. The conclusions reached are conveniently detailed at the end of each chapter and are summarized at the end of the volume, but no new theory of the mechanism of urine transport from kidney to bladder is presented. The experimental results are stimulating, but the limitations of the manometric method need constantly to be borne in mind, so that the book contains much of interest to the physiologist and

experimental urologist, but may be of limited value to most clinicians.

Outline of Fractures. 2nd ed. By John Crawford Adams, M.D.(London), F.R.C.S.(England). (Pp. viii+268; illustrated. 27s. 6d.) Edinburgh and London: E. & S. Livingstone, Ltd. 1958.

The first edition of this book was reviewed in these columns in June 1957 ("Proceedings," **50**, 436). The appearance of a second edition so soon is proof of the book's popularity. Apart from the section on the spine, there are no major alterations.

Rehabilitation of the Hand. By C. B. Wynn-Parry, M.B.E., M.A., D.M., D.Phys.Med. (Pp. vii+273+17; illustrated. 45s.) London: Butterworth & Co. (Publishers) Ltd. 1958.

Interest in disabilities of the hand is still gaining momentum in Great Britain and the Second Hand Club is flourishing. Wynn-Parry's important book, published on the crest of this wave, makes a large contribution to the detailed knowledge of this subject. Anatomy and physiology are dealt with in a functional and interesting way, and the pathological anatomy is refreshingly clear and concise. There are separate chapters on tendon injuries, nerve injuries, hand stiffness, the rheumatoid hand and upper limb weakness. The chapter on electrodiagnosis describes in 20 pages and in sufficient detail all the modern views on this subject. In this chapter it is made obvious that the doctor who has to deal with nerve injuries cannot rely on such old-fashioned investigations as R. of D.; there is a great deal more to know than that.

It is a little disappointing that considerable emphasis is placed on passive treatment (e.g. oil massage and stretch splinting), in the management of immature deformities which respond so satisfactorily to a repetitive exercise programme. Perhaps one still expects the enthusiastic superactive programme that characterized the R.A.F. in wartime.

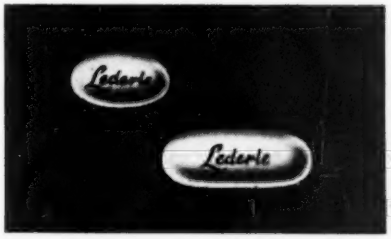
This criticism is the only one that can be levelled at a volume that is not only full of information, right up to date and beautifully produced, but also includes a delightfully sound chapter on the principles of reconstruction of the hand by D. Brooks.

The final chapter on resettlement describes all the facilities available in this country for the intelligent resettlement of persons with residual disabilities that preclude return to normal work. It is a comprehensive survey and yet the author has succeeded in condensing it all into 16 pages.

Dr. Wynn-Parry is to be congratulated on producing such a clear, complete and authoritative guide for a rapidly growing group of persons interested in rehabilitation of hand disabilities.

Physical Examination of the Surgical Patient. By J. Englebert Dunphy, M.D., F.A.C.S., and Thomas W. Botsford, M.D., F.A.C.S. 2nd ed. (Pp. xv+375; illustrated. 56s.) Philadelphia and London: W. B. Saunders Company. 1958.

The second edition of this popular American textbook differs only slightly from the first, the most important difference being the addition of short chapters on the taking of the history and on cancer detection. The previous edition was illustrated entirely by drawings, chiefly line drawings, and the few photographs now included hardly compensate for the breaking of the illustrative continuity. The work successfully combines the functions of a textbook on the technique of physical examination of the surgical patient and an elementary textbook of differential diagnosis.



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